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CORRECTION: The authors of "The Hospital Emergency Incident Command System – Are You Ready?" in July 2003 issue (2003;86:193-5) were Achyut Kamat, MD, Gary Bubly, MD, and Liudvikas Jagminas, MD.

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Feeling Comfortable With Not Knowing



Patients like to know what's wrong with them. That seems obvious. Yet, more than that, they like to know their *diagnosis*; that is, the name assigned to their condition, even if it's untreatable. That was not obvious to me until I read it somewhere. Someone pointed out that patients felt more secure, more comforted, to have a name for their disorder, as if naming the beast provided sense and order to their situation.

In much of medicine, living diagnoses can be made most of the time and are often, perhaps even most of the time, definitive. One can "prove" the existence of coronary artery disease with a variety of tests, biopsy a tumor, or an organ, to arrive at a "tissue diagnosis," obtain an imaging study or an endoscopy, or a wide variety of diagnostic tests that are frequently definitive. Neurology, like rheumatology, however, tends to have syndromes. One has Parkinson's disease clinically if three of four criteria are met in the absence of an alternative explanation or atypical features, much like having lupus or rheumatoid arthritis. Non-specific blood tests are helpful in rheumatology but not neurology. A variety of tests demonstrate that one does not have Parkinson's disease, but none prove the diagnosis.

As in rheumatology, many disorders don't fit the consensus criteria and we are left to decide whether these cases are atypical presentations of well-known disorders or "new" or very rare disorders not widely known. Over the years I've gotten quite comfortable, perhaps excessively comfortable, in *not* making a diagnosis. I have to take some time to explain to the patient why I don't know the diagnosis, why I can't make the diagnosis and why, despite not having a name to hang a prognosis and treatment (usually none anyway)

on, I can still create a treatment plan and prognosis that would be as good as that made by a better clinician who might render an actual name for the condition.

I see patients who primarily have neurodegenerative disorders and these share so many common attributes that whether I call a condition "multi-system atrophy," "atypical progressive supranuclear palsy," or "primary progressive subcortical gliosis," is far less important than saying, "It's not Parkinson's disease," which translates, in practical terms, to, "We will try some of the medications that are used in PD, but they're unlikely to work and if they do work the improvement will be limited, so we should not be aggressive."

A neurology resident recently commented to the fellow who works with me, "Dr. Friedman didn't know the diagnosis," as if this was a startling bit of information. She assured him that I not infrequently said this. However, I was quite startled myself when one of my internal medicine colleagues, a person I hold in high esteem, seemed surprised almost to the point of being dumfounded when we shared a case in which I openly shared my lack of knowledge. She was not impressed with the honesty but rather with the ignorance. In her mind, I work in an arcane area where all the diagnoses, short of stroke and epilepsy, are fairly rare, and, if one specialized in the rare, then one would most likely know all the diagnoses. But, as I tell my patients, the brain isn't like the other organs. We can't get pieces to look at under the microscope. While our imaging techniques have advanced dramatically in the last 25 years, most of the neurodegenerative disorders don't have imaging abnormalities. The brains look normal until stained and enlarged. In fact, many disorders have

normal histology and the abnormalities are presumably restricted to biochemical pathways present in only some part of the brain.

As we learn more about disease pathogenesis, it turns out that some, maybe all, of the neurodegenerative disorders are due, at least in part, to genetic abnormalities, even those that emerge in the elderly. In addition, the more we learn about the inherited diseases we've known for centuries, like Huntington's disease, the more we learn that while one genetic abnormality may determine disease, it only partly determines phenotypy. We are identifying people with diseases associated with genetic anomalies not seen before, suggesting that these diseases have not been diagnosed before. The journals frequently contain case reports of people with degenerative disorders not previously recorded.

A few years ago I presented some cases at grand rounds to a visiting dignitary whom I had invited. The classic grand rounds of 100 years ago is still an unsurpassed teaching format. I chose the cases because each one had me baffled. The guest diagnosed the first two as both having a disorder I was quite familiar with, to which I had even contributed an oft-cited clinical paper. I followed one of the patients for several years thereafter, and she never evolved the criteria necessary for the diagnosis, and the other was lost to follow up. I told the patients that Dr. X, one of the best in the world, thought they had progressive supranuclear palsy, but that I wasn't convinced. I think honesty is the best policy, even when patients need the security of a name, an identity for their enemy. I also hate being wrong.

— JOSEPH H. FRIEDMAN, MD

The Devil Is In the Details



Numbers are awesome things. Certainly the invention of numbers—along with the contrivance of such primal essentials as the wheel, the plow and the kindling of fire—must be regarded as almost the most fundamental of human discoveries. The act of counting taught mankind that numbers can faithfully represent larger entities such as cattle or sheaves of wheat or human chattel; and that each number was no more, nor less, than a discrete element in an endless sequence of evenly spaced numerals. Numbers therefore can be surrogate to tangible things; and numbers alone, without representing anything real, can also do astonishing things.

Numbers can be faithfully added, subtracted or can participate in other arithmetical maneuvers such as multiplication and division. Yet despite the preeminently neutral quality of numbers, mankind has seen fit to discern mystical qualities in certain numerals, somehow endowing them with magical properties and wondrous attributes. Many sages have concluded that numbers are the outward manifestations of life's fundamental forces; that numbers actually govern the laws of space and time, while defining the rhythms of the physical universe. Numbers, they have asserted, are the tangible face of ultimate truth and hence can represent both good and evil.

Numbers such as 3, 13 and 40 have each become elaborate metaphors for both secular and religious beliefs. Plato described numerology, the study of these hidden attributes within bland numbers, as the essence of cosmic and inward harmony.

Those beholden to numerology believe that these special numbers carried latent powers which are unleashed when the particular number is uttered or written. Great authority may therefore accrue to anyone aware of these hidden powers embedded within certain numbers.

Over the centuries, for example, many scholars have contemplated the numeral six. St. Clement of Alexandria noted that the world was created in six days. Furthermore, the six-pointed Star of David, sometimes called the Seal of Solomon, consists of two intersecting equilateral triangles that numerologists regard as a sacred hexagram representing the six orientations of space [the four points of the compass as well as the nadir below and the zenith above].

In the last Book of the Bible, Revelation, there appears a cryptic reference to the underlying meaning of the number six. In Chapter 13, lines 17-18, Saint John describes a blasphemous beast arising from the sea, with seven heads and ten horns. And then later he beholds yet another beast, also with evil intent. The chapter concludes with these portentous but ambiguous words: "Let him that hath understanding count the number of the beast: for it is the number of a man; and his number is six hundred three score and six."

This number, 666, is believed by many to be the incarnate numerical signature of Satan. And it is therefore a number to be feared and either denied or assiduously avoided.

South Korea had recently assigned troops to the Iraqi war. The number of troops sent to the Middle East was determined strictly by military need; but at the last moment someone noted

that the contingent consisted of 666 soldiers. Seven infantrymen were hastily added and thus there were now 673 soldiers in transit, a safer number which carried no currently known hint of the Devil.

The American highway system employs numerals to designate its component roads. Some of these numbered roads [such as Routes 95, 1 and 40] are both well-known and well-traveled. But in the drought-burdened northwest corner of New Mexico one encounters a roughly north-south oriented two-lane road called Route 666. Locally it is known as the Devil's Highway. This desolate stretch of highway begins in Gallup, New Mexico, as a northerly branch of Route 40, then it winds through desert-like Navajo territory. This is a lonely road with virtually no intersections for 95 miles until it reaches Shiprock, New Mexico. Route 666 then bends to the west and traverses the poorly populated southwest corner of Colorado for a dismal 60-mile stretch of highway just west of Mesa Verde National Park. It then crosses into Utah and ends in Monticello, Utah [population, 1958], southeast of Canyonlands National Park. Scattered along the upper reaches of Route 666 are a small number of gambling casinos where three legitimately drawn sixes in a poker game still pay off as handsomely as in plush Las Vegas.

Highway triple-six, in truth, is an undistinguished dreary back-road of New Mexico, Colorado, and Utah, noted for little other than its reputation as the Devil's Highway. Admittedly the number of traffic mishaps [87 recorded accidents and 16 vehicular deaths per 100 miles per year] is measurably greater than on neighboring roads; but few police officials would believe that the elevated mortality rate was due solely to the number assigned to the road. Local citizens, however, ascribe the vehicular mortality to the Devil—and tequila.

Over the years the citizens in the towns traversed by Route 666 have petitioned to have its number changed. Under the lead of New Mexico's current governor, officials from the three states traversed by Route 666 have pleaded with federal highway officials to alter the number 666, thus removing the satanic cloud contaminating their highway. They point out, for example, that Route 666 is not only their highway; it is their *only* highway.

On May 31, 2003, Route 666 was finally changed to Route 491. Epidemiologists are now eager to note whether the naming-change will have a salutary effect upon the road's vehicular mortality rate in coming years. They will obviously wonder whether Satan's adopt-the-highway program, now eliminated, will reduce the mayhem on this highway formerly known as Route 666, or whether the effects of tequila will continue to prevail despite the removal of devilish influences.

Americans have a way of converting adversity into a tangible advantage. Bumper stickers and T-shirts, for example, have proclaimed our native resoluteness through declarative statements such as: "This car climbed Mount Washington: or "I survived the Blizzard of '78." It would be almost un-American not to issue T-shirts now stating: "Praise the Lord, I drove the length of Route 666 without a scratch."

— STANLEY M. ARONSON, MD, MPH

Implications of Lack of Concordance Among Oncologists For Evidence-Based Medicine Derived Clinical Guidelines

Gerald J. Elfenbein, MD

Probably the most important thing my first mentors at Johns Hopkins, Drs. Albert Owens and George Santos, told me in 1967 was to avoid tilting at windmills, like Don Quixote, because there were just too many of them. Sage advice, but sometimes advice that cannot be followed. Thirty-five years later, I participated in two separate oncology survey programs¹ in which case scenarios were forwarded by facsimile: How would I treat a given patient at a specific point in his/her malignant disease course? I was asked to choose one from several preset answers. The selected respondents were supposedly “experts” in medical oncology. They could be considered representative of the oncologists who sit on panels and establish clinical guidelines using evidence-based medicine. One would think that the results from these surveys would point to a single “best” treatment response in each circumstance because evidence-based medicine would define “best”. But this was not the case. I accumulated 54 consecutive reports from these surveys: for treatment decisions, concordance among clinical oncologists was low (Figure 1). On average, the first choice answer was selected only 50% of the time.

The second choice answer was selected only 50% of the frequency of the first choice, or 25% of the time, on average. This relationship holds for the third, fourth, fifth, and sixth choices, and describes a hyperbolic function with a zero asymptote. Although a majority or often a plurality “rules”, it is perfectly unclear to me what the “correct” answers were.

*...uniformity of
treatment does not assure
quality of care.*



As we practice medicine on a daily basis, we have grown accustomed to a high level of concordance in the interpretation both of imaging studies and of preparations of pathologic specimens. Furthermore, we increasingly expect a single “best answer” for each case scenario. We ascribe to the fundamental belief that evidence-based medicine provides clinicians with practice guidelines to make appropriate decisions for their patients in each circumstance, which

should be reflected by concordance in surveys.

What does the lack of a high level of concordance in treatment decisions by oncologists teach us about these beliefs and expectations?

The trivial answers are that the scenarios may have been inaccurate or incomplete; the survey questions may have been ambiguous; or the answers may have all been inappropriate or even incorrect. As tempting as these answers, in all probability none are correct. What is more likely is that evidence-based medicine has limitations that have not been explored thoroughly nor presented clearly and that practice guidelines, as derivatives of evidence-based medicine, are not sufficiently reliable to assist clinicians in making decisions for their patients in many scenarios with a high degree of uniformity.

Evidence-based medicine has established a hierarchy of reliability of data published in the literature, with least reliable being case reports and small series without historical controls (evidence level five) and most reliable being large, **randomized, controlled trials (RCT)** and meta-analyses (evidence level one; see Figure 2). On the surface, this hierarchy seems reasonable. But it should not be considered absolutely authoritative. By their very nature, RCT have very stringent entry criteria, which translate in clinical research to studies of a very restricted subpopulation of patients with a specific disease, i.e., the eligible patients display a very narrow range of variability within the disease spectrum, thus limiting applicability to the rest of the spectrum. Lacking results from patients-at-large, clinicians are forced to extrapolate data to make clinical decisions. Extrapolation is fraught with a great chance of error. Further, the design of RCT (not their statistical underpinning) may be flawed (such as the selection of the control arm treatment), leading to misinterpretations of the data

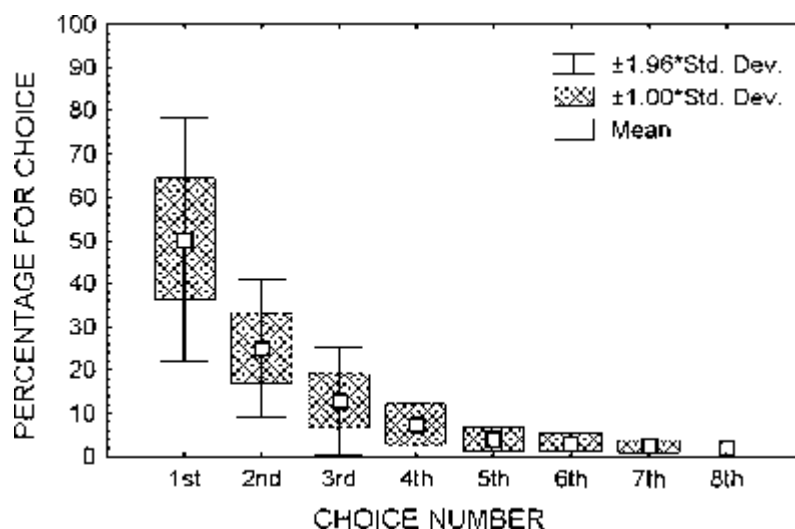


Figure 1. Concordance among Oncologists in Decisions Concerning Treatment Choices for Case Scenario Patients. Note the striking hyperbolic relationship.

Level 5 (lowest)	Case Series
Level 4	Historical Controls
Level 3	Comparative Cohort Study (contemporary controls)
Level 2	Randomized Controlled Trials (RCT) small in size
Level 1 (highest)	RCT, large enough or Meta-analysis

Figure 2. Levels of Evidence (adapted from Sackett, 1989).²

and subsequent conclusions about what to do, which potentially may be the opposite of what actually should be done. Moreover, RCT may be terminated too early to find a difference (beta error) or, even worse, reported prematurely because eager study investigators want to share their findings.³ Finally, RCT may select endpoints that are inappropriate for the scenario being studied. An example of such an endpoint is overall survival.

For a scenario in which the patient is terminally ill and no other therapy is of any known value in prolonging life, testing a new drug or treatment modality in a RCT compared to no therapy at all and then observing overall survival for improvement to justify using the drug or treatment is quite reasonable.

However, when the patient is receiving first line therapy for a malignancy (such as adjuvant therapy for high risk, primary breast cancer) that has a natural history of prolonged duration and if salvage therapy can prolong life after relapse has occurred, then examining overall survival is not at all justifiable because overall survival is determined not just by first line therapy but also by subsequent salvage therapies as well as other determinants. Overall survival is at least one step removed from first line therapy and requires a very long observation period, perhaps 5 to 10 years, before it may be evaluated properly to minimize beta error. Disease-free survival is the more appropriate endpoint because it is directly related to first line therapy. Moreover, it defines the treat-

ment-free interval for patients who do relapse and the population of patients that have the potential of being cured. What needs to be established is a hierarchy of endpoints that are directly attributable to the therapy under investigation and not to potentially multiple, intervening steps (Figure 3). If, for instance, disease-free survival is equivalent for both arms of a study, then the next level of

evaluation could be quality of life, followed by cost of therapy.

Finally, the durability of validity of the conclusions drawn from RCT (also called phase III trials) and meta-analyses has come under close scrutiny.⁵ This evaluation found that phase II (levels three and four) trial findings are at least as durable, if not more, than phase III trials and meta-analyses (levels one and two). If evidence-based medicine aims to improve the quality of care via guidelines that would result in concordance of decisions and uniformity of treatment, then evidence-based medicine cannot and will not succeed for at least one very good reason. There are far too many clinical scenarios (cf. Don Quixote's windmills) than evidence-based medicine could hope to address by RCT, let alone meta-analyses. Researchers have neither the time nor money to study all the scenarios. Moreover, when evidence-based medicine concludes that "there is no evidence to support the use of a specific treatment" or "a specific treatment has no value," in many cases this is because there are no level one or two studies and level three and four studies have been ignored or, worse, discounted as "weak" science. Consequently, these statements often lead to denial of insurance funding of treatment because the treatment may be not "appropriate". Let's not reproduce Galileo's scenario.⁶ He did not have an RCT to prove that the planets revolved about the sun not the earth, and it cost him dearly. The most important leaps forward in knowledge are often based on level three and four evidence from phase II studies.

We need a more mature attitude towards and better understanding of evidence-based medicine, so that it may serve, not disserve, our patients. The clinical guidelines generated from evidence-based medicine will be of greatest utility only when they are put into proper perspective, because uniformity of treatment does not assure quality of care. Patients are individuals with unique clinical scenarios; their treatment plans need to be guided by all of the medical literature and individualized to their particular circumstances.

1	Cure rate (restoration to survival expectation of age cohort)
2.	Disease-free survival at 5 years after therapy
3.	Overall survival at 5 years after therapy
4.	Median duration of remission or median duration of response
5	Median duration of survival
6	Quality of life while alive
7.	Cost of treatment per extra year of life
*Rank ordered according to stringency (for proof of principle) and value to patient (for proof of efficacy).	

Figure 3. Primary Endpoints for Oncology Clinical Trials (adapted from Elfenbein, 2001).⁴

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This issue of *Medicine & Health/Rhode Island* is dedicated to the memory of Adele R. Decof, a loving wife, mother, grandmother and good friend, who lost her battle with breast cancer after eight years of valiant effort. Mrs. Decof never lost her optimism, determination or need to help others in the fight against this pernicious disease. Her legacy is the inspiration behind the formation of the Adele R. Decof Foundation by the Decof family to carry on that fight in her name and to improve life for all cancer victims to come after her. The Adele R. Decof Foundation joined with the Roger Williams Medical Center to fulfill the vision of what the best cancer treatment center should look like: caring, cutting-edge, accessible and effective, all at once. At the Adele R. Decof Cancer Center that vision is put into practice. Innovative research translates into improved patient treatment, delivered with compassionate and personalized care. In this way, the Decof family is spreading Mrs. Decof's optimism "that better days lay ahead for cancer victims and their families."

Andrea Decof
Adele R. Decof Foundation



Novel Approaches In the Treatment of Multiple Myeloma

Mehrdad Abedi, MD, and Gerald J. Elfenbein, MD

Plasma cell dyscrasias are a spectrum of B cell derived, plasma cells abnormalities. At one end they include **monoclonal gammopathy of undetermined significance (MGUS)** and extramedullary plasmacytomas and at the other end are the plasma cell leukemias. **Multiple myeloma (MM)** is the prototype of a tumor of differentiated plasma cells frequently accompanied by **monoclonal (M)** protein production and either diffuse osteoporosis or single or multiple osteolytic bone lesions. It accounts for approximately 1% of all malignant diseases and 10% of hematologic malignancies. The annual incidence of myeloma is 3–4 per 100,000 people.

The median age of patients with MM is 65 years. The incidence is slightly higher in males than females, twice as high in African Americans as in whites, and lowest in Asian populations. MM mortality rates are increasing in the elderly. These increases may be related to differences in the gene pool of successive elderly cohorts, as adversity to human survival (mainly mortality due to infections) has declined drastically.

ETIOLOGY

Both genetic and environmental factors have been implicated but the cause of MM remains unknown. A genetic predisposition is suggested by re-

ports of familial clusters of two or more first-degree relatives with MM and also by a significantly higher incidence of MM among African Americans. Environmental risk factors may be exposure to radiation, sheet metal work, and mineral oils used as laxatives or for dermatitis.

Clinical Manifestations, Diagnosis, and Prognostic Factors

The clinical features and etiology and management of manifestations of MM are summarized in Table 1.

The diagnosis of MM needs a combination of clinical, pathological and laboratory evidence. Table 2 summarizes the method of evaluating patients with MM. Table 3 summarizes the criteria for making the diagnosis.

Without therapeutic intervention the median survival is approximately 7 months, which increases to 2.5–3 years with conventional chemotherapy. Only 3.5% of patients survive more than 10 years. The Durie-Salmon clinical staging system attempts to estimate the tumor burden in the patient. This staging system is mostly based on the manifestations of the disease and presence of renal failure (Table 4). Patients with a low tumor load and creatinine <2 mg/dl (stage IA) have a median survival of approximately 5 years, whereas patients with a high tumor load and renal sufficiency (stage IIIB) have a median survival of 15 months.

Beta-2 microglobulin ($\beta 2M$) and C-reactive protein (CRP) levels have prognostic significance in MM. Since the predictive value of CRP and $\beta 2M$ are independent, a combination of these two parameters has been used for stratification of patients into risk groups (Table 5).

Additional risk factors include the following: The **plasma cell labeling index (PCLI)** measures the proliferative activity of plasma cells. The median survival of MM patients with a PCLI < 3% is 56 months, compared with 19 months for those with a PCLI $\geq$ 3%.

Table 1: Clinical Features and Etiology and Management of Manifestations of Multiple Myeloma

Clinical Feature	Etiology	Management
Anemia	High levels of IL-6, bone marrow replacement and dilutional due to high M protein	Erythropoietin
Bone lesions	IL-1 β , also IL-6 and TNF- β	Bisphosphonates, morphine derivatives
Hypercalcemia	Bone destruction	Urgent hydration, bisphosphonates, calcitonin
Amyloidosis	Insoluble M protein cardiac, renal, and neurologic problems	Eradication of malignant clone
Hyperviscosity	Mainly in IgA myeloma and IgG $_1$ myeloma	Plasmapheresis
Dehydration	Hypercalcemia, hypoalbuminemia, IL-6 secretion	Control of hypercalcemia, hydration
Renal failure	Myeloma kidney, light chain deposition disease, IL-6	Treatment of myeloma
Neurologic symptoms	Central: Compression by tumor or bone fragment of spinal cord Peripheral: Amyloidosis	Local irradiation with or without chemotherapy
Infection	T-cell deficiency: Fas ligand on plasma cells (?) B-cell deficiency: TGF- β	Therapy: prophylactic antibiotics with initial cytotoxic treatment, IVIG

Table 2. Evaluation of Patients with Suspected Multiple Myeloma

- Complete history and physical
- Blood work: complete blood count with differential, electrolytes, BUN, creatinine, calcium, phosphate, urea acid, LDH, alkaline phosphatase, serum protein electrophoresis, quantitative immunoglobulins, serum immunoelectrophoresis, $\beta 2$ -microglobulin ($\beta 2M$), C-reactive protein (CRP).
- Radiographic survey of the bones
- Bone marrow aspirate and biopsy with plasma cell labeling index (PCLI) and cytogenetics
- MRI of the head, spine, and pelvis in the case of neurological signs and symptoms including severe back pain or for solitary plasmacytomas

Table 3. Criteria For The Diagnosis Of Multiple Myeloma**Major Criteria**

Plasmacytoma on tissue biopsy

Marrow plasmacytosis $\geq 30\%$

Monoclonal protein

IgG > 3.5 g/dlIgA > 2 g/dlBence-Jones protein ≥ 1 g/24 hr**Minor Criteria**

Marrow plasmacytosis 10–29%

Monoclonal protein present but less than the levels defined above

Lytic bone lesions

Decrease in uninvolved immunoglobulins

IgM < 50 mg/dlIgA < 100 mg/dlIgG < 600 mg/dl

The diagnosis is confirmed with at least one major and one minor criterion or at least three minor criteria

Unfavorable karyotypes, e.g., translocations or abnormalities involving 11q or partial or complete deletion of chromosome 13 reflect a particularly poor outcome in patients receiving autotransplants. Elevated LDH levels are associated with a median survival of only 9 months and a low response rate (20%) to standard chemotherapy. Plasmablastic myeloma ($\geq 2\%$ plasmablastic myeloma cells in the bone marrow), presence of monoclonal plasma cells in the peripheral blood and especially plasma cell leukemia (an absolute plasma cell count in the peripheral blood of $\geq 2.0 \times 10^9/L$ are among the poor prognostic factors.

On the other hand, patients with smoldering myeloma (serum myeloma protein level > 3 g/dl but < 4.5 g/dl and $> 10\%$ atypical plasma cells in the bone marrow, without anemia, renal insufficiency, hypercalcemia, or multiple skeletal lesions) are usually asymptomatic and have a better prognostic outcome. They should not be treated until there is clear evidence of disease progression or symptomatic disease (median time to progression to myeloma is 26 months). MGUS is characterized by the presence of a serum M protein of < 3 g/dl and $< 10\%$ plasma cells in the bone marrow with no or only small amounts of Bence-Jones protein in the urine, absence of lytic lesions, anemia, hypercalcemia and renal insufficiency, and most importantly stability of the M protein. The majority of patients with

MGUS die of unrelated causes; only 11% progress to MM. The median (range) interval from recognition of the M protein to the diagnosis of MM is 10 (2–29) years. Solitary plasmacytoma of bone is uncommon and represents 3–5% of patients with plasma cell dyscrasias. The most common symptom at diagnosis is pain. The diagnosis is based on finding tumor masses consist of monoclonal plasma cells with no other lesions on skeletal survey or MRI, a normal bone marrow and absence of an M protein in blood and urine; or, if present, therapy for the solitary lesion should result in disappearance of the M protein. Overt MM develops in approximately 50% of these patients with evidence of progressive disease within 3

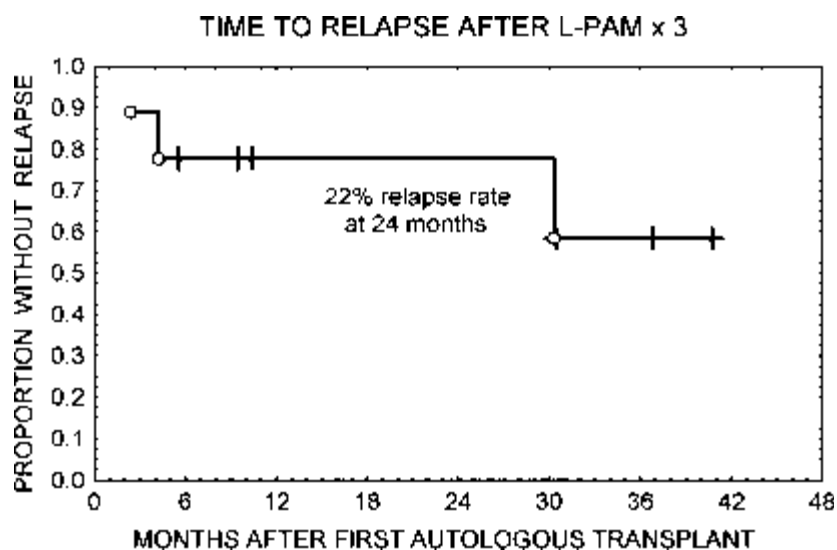


Figure 1. Time to Relapse of Multiple Myeloma after Triple Transplant

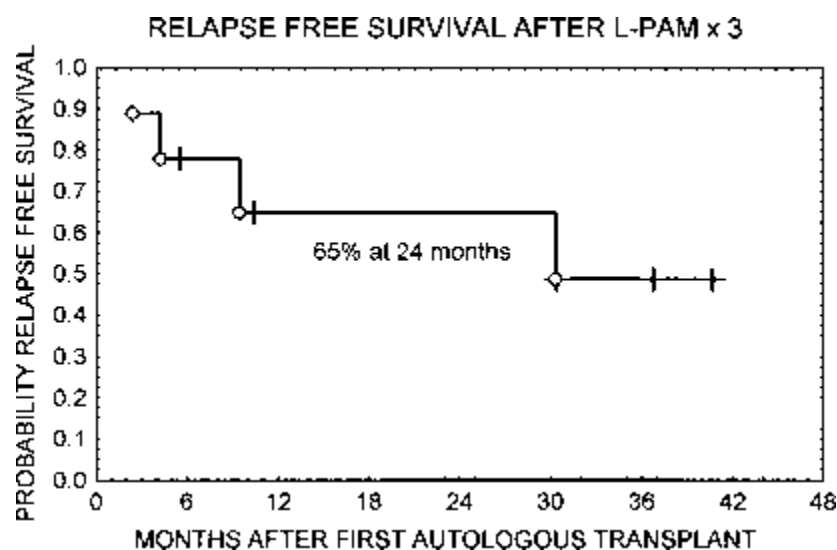


Figure 2. Relapse Free Survival for Multiple Myeloma after Triple Transplant

Table 4. Durie-Salmon Staging System

- **Stage I: Low tumor mass ($<0.6 \times 10^{12}$ myeloma cells/ m^2)**
All of the following:
Hemoglobin > 10 g/dl
IgG < 5 g/dl; IgA < 3 g/dl; Bence-Jones < 4 g/24 hr
Normal calcium level
No or only one lytic bone lesion
 - **Stage II: Intermediate tumor mass ($0.6-1.2 \times 10^{12}/m^2$)**
Not fitting stage I or III
 - **Stage III High tumor mass ($>1.2 \times 10^{12}/m^2$)**
Any of the following
Hemoglobin < 8.5 g/dl
IgG > 7 g/dl; IgA > 5 g/dl; Bence-Jones > 12 g/24 hr
Calcium level > 12 mg/dl (adjusted for albumin)
Multiple lytic lesions
- A. BUN ≤ 30 mg/dl, creatinine ≤ 2 mg/dl
B. BUN > 30 mg/dl, creatinine ≥ 2 mg/dl

years in two-thirds of the patients. Radiotherapy (4,000–5,000 cGy) has been considered the treatment of choice.

APPROACH TO THERAPY FOR SYMPTOMATIC MYELOMA

Patients with asymptomatic myeloma usually have low tumor burden and should be monitored closely. Symptomatic patients or those with anemia, recurrent infections, hypercalcemia, or renal insufficiency require treatment. For patients requiring treatment, sufficient evidence from both the French randomized and a pair-mate comparison is available that high dose chemotherapy is superior to standard dose treatment in

terms of complete response rate and event-free and overall survival. Peripheral blood stem cell transplants can be performed safely up to age 70 and in patients with renal failure as well. Usually patients will receive one to three cycles of chemotherapy prior to stem cell mobilization to improve the patient's general condition and to attain a significant tumor reduction. This is best achieved with the VAD regimen. Pulse high dose dexamethasone may be superior because of the rapidity of response and its stem cell sparing capacity. Patients who are not candidates for high-dose chemotherapy should be treated for at least 12 months or until a plateau phase (stable M pro-

tein for at least two months) has been obtained. Because of the high treatment-related mortality, allogeneic bone marrow transplantation should probably only be performed in patients with poor prognostic factors or failure to achieve at least a 50% reduction in M protein.

CYTOTOXIC THERAPY Standard Dose Therapy.

Oral melphalan and prednisone have remained the standard therapy for symptomatic myeloma. They provide control of symptoms and tumor reduction by $\geq 50\%$ in approximately half the patients. One of the most popular combination regimens is **vincristine added to Adriamycin[®] and prednisone (VAD)**. There is no clear advantage of combination chemotherapy over melphalan plus prednisone. VAD-based regimens in previously untreated myeloma patients result in a 55% response rate with near-maximum response occurring after two cycles of treatment. High dose dexamethasone alone in refractory myeloma has 15% less response rate but is equally effective as VAD in terms of survival. By adding **cyclophosphamide to VAD (CVAD)**, 40% of VAD-resistant myeloma patients show an objective response.

Patients responding to standard chemotherapy have a much better survival than nonresponders (43 months vs. 19 months) with no survival advantage for complete responders over partial responders. Most responders attain a plateau phase, that is, a state of tumor quiescence. The duration of this plateau phase is variable and has direct survival impact with longest survival in patients with prolonged plateau phase. Response rate for refractory/relapsed MM remains very low. A recent report suggest that a regimen including **doxil (D)**, **vincristine (V)**, **dexamethasone (d)** and **thalidomide (T) (DVd-T)** for relapsed/refractory MM can be very effective in this group.

Autologous Stem Cell Transplantation.

Because minor dose increases in alkylating agents, as used in the combination chemotherapies, had not resulted in improvement of overall survival, it appeared worthwhile to try more pronounced escalation. This was first pi-

Table 5. Stratification Of Myeloma Patients By Risk Factors

	CRP	$\beta 2M$	Median survival (mos)
Low risk group	< 6 mg/L	< 6 mg/L	54
Intermediate risk group	> 6 mg/L	< 6 mg/L	27
High risk group	> 6 mg/L	> 6 mg/L	6

Table 6. Results of Standard Treatment and Autotransplants in Myeloma

Treatment Regimen	No. Pts.	Complete Response (%)	Median Survival (mos)	5-Year Survival (%)
Dexamethasone alone	112	-	36	N/A
VAD	175	-	36	30
VMCP/VBAP	115	-	36	30
VBMCP	220	-	30	26
Melphalan/Prednisone	335	-	26	18
Autotransplants				
Melphalan/TBI	100	22	60+	52
Melphalan	195	53	54	40
Double transplants	123	40	62	60

Abbreviations: V - vincristine, M - melphalan, C - cyclophosphamide, P - prednisone, B - BCNU, A - Adriamycin[®], D - dexamethasone, TBI - total body irradiation

Table 7. Promising Future Therapies

- CC5013 (IMiDs) is a derivative of thalidomide and preliminary data suggests that it may be more effective than thalidomide in treating cases of multiple myeloma.
- PS341 (Proteasome Inhibitors). The proteasome inhibitor PS-341 is another active agent in refractory myeloma. A recent multicenter trial with PS-341 in patients with refractory myeloma showed a response rate of 50%.
- As_2O_3 has been shown to inhibit the growth of myeloma cell line in-vitro.
- Fludarabine added to VAD.
- M-12 therapy in plateau phase MM is associated with improvement in blood immune cells and in clinical responses including durable CR albeit in a minority of patients.
- Dendritic cell vaccination
- 2-methoxyestradiol
- Farnesyl transferase inhibitors
- Flavopiridol
- Angiogenesis inhibitors

loted by McElwain et al. using a dose of 100–140 mg/m² of melphalan. Three of 5 previously untreated patients achieved a biochemical and bone marrow complete remission, compared to a 3% complete response rate with standard therapy. However, the procedure-related mortality was high at 15–20%, mainly due to prolonged aplasia, a problem correctable with a bone marrow transplant. Bone marrow transplantation allowed further intensification of therapy: the dose of melphalan could be escalated to 200 mg/m² or total body irradiation could be added to melphalan at 140 mg/m². Further progress was made by supporting high dose chemotherapy with mobilized peripheral blood stem cells (PBSC) to shorten aplasia further. With peripheral blood stem cell support, transplant-related mortality is <5% and tandem transplants are feasible. After high dose chemotherapy and autologous blood stem cell transplant, 30% achieve a defined complete response (CR; absolutely no evidence of residual disease) with median duration of event-free and overall survival of 26 and 41 months, respectively.

The most important prognostic variables for event-free and overall survival after autotransplant are cytogenetics, duration of standard-dose therapy, and the β 2M level prior to the first transplant. Although it is still unclear whether MM patients can be cured with autotransplants, based on the lack of a plateau in the survival curves, it seems likely that in the low-risk group of patients (i.e., those with favorable cytogenetics, <12 months of preceding standard therapy, and low β 2M levels prior to transplantation) a plateau

is starting to form. Approximately 20–30% of these patients (8–10% of all patients) may be cured.

Recently thalidomide, an agent with antiangiogenic properties, has emerged as an active agent for relapsed and refractory myeloma.



Tandem transplants: Double transplants

Barlogie et al. at the University of Arkansas advocate tandem autologous stem cell transplants to improve CR rates and survival. In a study of 231 patients with newly diagnosed myeloma, they showed that more than 70% of patients are able to go through induction therapy and both transplants. Mortality rates were 3% during induction, 1% with the first transplant, and 4% with the second transplant. By intent-to-treat analysis, the CR rate was 26% with the first transplant and 41% after the second transplant. Overall survival with this approach was 68 months. Data from 4 different randomized trials on this treatment strategy were presented recently. The most mature trial reported an increase in response rates and event-free survival with tandem transplantation. The final results of these trials will clarify this important issue.

Triple transplants

To decrease the toxicities of high dose therapy even further and to increase dose intensity of melphalan delivered, we initiated a pilot, phase I/II study in which three courses of melphalan, also known as **l-phenylalanine mustard (l-PAM)**, at 100mg/m² were given at 21-day intervals (l-PAMx3). One day after each treatment, previously collected PBSC were infused. Nine consecutive patients with MM were enrolled to determine the tolerance to and efficacy of the 3 transplants in the outpatient setting. Five pts were judged to be standard risk (at least a partial response to 4 cycles of VAD) and 4 patients, who required additional chemotherapy (the DCIE regimen; *Brit J Hematol* 1997;96:746-8) to achieve at least a partial response, were adjudged to be at high risk. Post-transplant consolidation therapy with interferon, thalidomide, or rituximab was given. Recovery of blood counts after the last course of therapy was at a median of 10 days for granulocytes > 500/ μ L and 19 days for platelets > 20,000/ μ L. At a median follow-up for survivors of 24 months, Kaplan-Meier actuarial estimates are: 1) probability of relapse – 22% (Figure 1), 2) relapse free survival – 65% (see Figure 2), and 3) overall survival – 65%. Standard risk patients have done considerably better than high risk patients (data not shown). Taken together these results are comparable to those reported by the ABMTR for single autologous transplants with 200mg/m² of l-PAM. The major differences in our approach are that it is delivered in the outpatient setting and it delivers 50% more melphalan in the same time period (2 months) as it takes to recover from a single transplant. Furthermore, the patients tolerated post-transplant consolidation.

Consolidation therapy after transplant

Several approaches have been suggested after autotransplant to eliminate minimal residual disease in order to prevent clinical recurrence. These include interferon, thalidomide (with or without dexamethasone), monoclonal antibodies, or combination chemotherapy. It is too early to determine if any of them will have an effect on survival. Some are

discussed briefly below along with an interesting new drug for MM.

Interferon-alpha

Encouraging results had been reported with interferon-alpha therapy as maintenance therapy after 12 cycles of standard treatment with prolongation of response and survival in MM patients responding to conventional chemotherapy sparking interest in using interferon after transplant even though subsequent studies failed to show a survival advantage. Prolonged interferon-alpha treatment prior to autologous transplantation makes collection of adequate amounts of peripheral stem cells very difficult.

Thalidomide with and without dexamethasone

Recently thalidomide, an agent with antiangiogenic properties, has emerged as an active agent for relapsed and refractory myeloma. In the first trial of thalidomide in relapsed myeloma most patients had failed stem cell transplantation. The overall response rate defined as a decrease in monoclonal protein levels by 25% or more was 32%. An update to this study confirms the activity of thalidomide in 169 patients with relapsed myeloma with overall survival at 2 years of 48%. Several similar studies have confirmed these results with response rates between 25% to 35% for relapsed myeloma. The median response duration is approximately 9 to 12 months. The mechanism of thalidomide antitumor activity and teratogenicity is still unclear and may also be related to immunomodulation, inhibition of tumor necrosis factor alpha production, free radical-mediated oxidative damage to DNA, or effects on cell surface adhesion molecules.

Monoclonal antibodies

The anti-CD20 antibody, rituximab, has been suggested as a candidate for treatment of MM. Myeloma cells are either negative or weakly positive for CD20 antigen. A group from Italy recently suggested that maintenance therapy with anti-CD20 monoclonal antibody after autologous stem cell transplantation in MM may be associated with early relapse. CD52 on the other hand is expressed on MM cell lines

and the preliminary results of at least one study suggests that the anti-CD52 antibody, alemtuzumab, significantly reduced tumor in 3 out of 4 chemotherapy resistance cases.

Clarithromycin (Biaxin®)

An unexpected and surprising activity of this agent in newly diagnosed and previously treated MM patients was reported recently by Durie et al. Patients received a dose of 500 mg of clarithromycin twice daily. Thirty patients were enrolled with the longest follow-up being 1 year. Six patients had a $\geq 75\%$ and seven had a $\geq 50\%$ reduction in M protein associated with improvement in clinical status. Responses were also observed in patients failing standard or high-dose chemotherapy.

SUMMARY

Despite all the new advances, treatment of multiple myeloma remains very challenging. Table 6 summarizes the outcomes of some of the commonly used treatments from different clinical trials. Treatment with conventional chemotherapy alone resulted in median survival from 18 to 30 months. Aggressive treatments like **VBMCP (vincristine, bleomycin, melphalan, cyclophosphamide, predisone)** although resulting in higher response rates, resulted in higher treatment-related mortality and did not have any effect on median and 5 year survival. High dose chemotherapy with stem cell support increased the median survival to around 60 months and resulted in durable complete responses in a significant number of the patients. Some of the newer and promising treatments for multiple myeloma are summarized in Table 7.

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New Therapeutic Approaches to Non-Hodgkin's Lymphomas

Jean-François F. Lambert, MD and Gerald J. Elfenbein, MD

Over the last thirty years, the yearly incidence of **non-Hodgkin's lymphomas (NHL)** has almost doubled to about 20 new cases per 100,000 people. The cause is mostly attributed to the more frequent use of organophosphate and thiazine pesticides in agriculture. Since 1995, this impressive increase has fortunately leveled off.

The classification of NHL has evolved markedly from the original Rappaport and Kiel classifications, based mostly on morphology, to the recent WHO-REAL classification using both morphology and cell surface phenotype to characterize each group. These groups can then be organized according to their clinical behavior. (Table 1)

Each of these newly defined entities has been further characterized by molecular biology and a specific gene translocation was defined for most of them. This is summarized in Figure 1.

For the last thirty years, the CHOP (cyclophosphamide (Cytosan®), hydroxydaunorubicin (Adriamycin®), Oncovin® (vincristine), and prednisone) regimen has been the first line of chemotherapy. In a landmark, intergroup, randomized study, three third-generation regimens challenged CHOP and were found to provide no additional disease-free or overall survival benefit than CHOP, but more toxicity.¹

Thus, despite unsatisfactory long-term remission rates, CHOP remains the only recognized treatment for advanced NHL.

MONOCLONAL ANTIBODIES²

Most B-cell lymphomas express CD20 on their membrane. A monoclonal antibody specific for CD20 was initially recognized to induce apoptosis in vitro and allow specific elimination by cytotoxic T-cells in vivo.³ A humanized anti-CD20, rituximab (Rituxan®), is now in clinical use. As a single agent in advanced relapsed NHL, rituximab produces a 30% overall (complete plus partial) response rate lasting for several months with very minimal toxicity.⁴ In combination with CHOP rituximab im-

proved relapse free survival and overall survival in de novo NHL.⁵ A recent, randomized study of 400 patients showed a significant advantage for CHOP plus rituximab compared to CHOP alone.⁶ A clear advantage was seen for event free survival (61% vs 43%) and overall survival (70% vs 57%) at 2 years follow-up. Furthermore, patients treated initially with CHOP plus rituximab, who relapse later, are still responsive to CHOP plus rituximab in 93% of the cases.⁷ Conceptually, rituximab should be even more efficacious in the setting of minimal

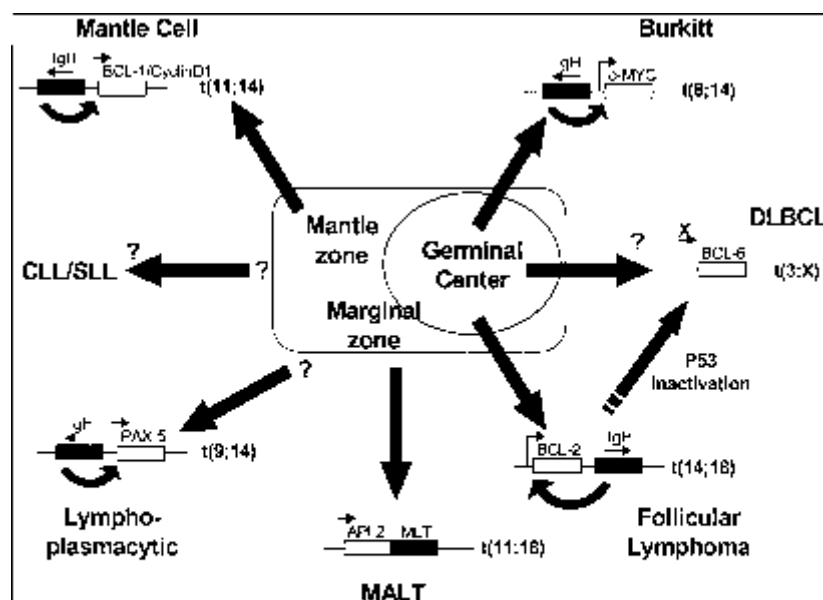


Figure 1. Molecular biology of B-cell lymphomas. In contrast to acute leukaemias, most of the lymphoma translocations result in the overexpression of an oncogene by a gene constructively expressed in the lymphocyte, mostly the heavy chain immunoglobulin gene (IgH). An exception is MALT lymphomas with a translocation t(11;18) producing a fusion protein, a chemoattractant similar to leukemia bands in vitro (eg. BCR-ABL in Philadelphia Chromosome in Chronic myelogenous leukemia).

Table 1. Survival at 5 years for major subgroups of the WHO-REAL classification of NHL.

Indolent NHL		Aggressive NHL	
>70%	50-70%	30-49%	<30%
Follicular	CLL/SLL	Diffuse LBCL	Peripheral T-Cell
Marginal zone of MALT type	Lympho-plasmacytic	Primary mediastinal LBCL	Precursor T lymphoblastic
Anaplastic large T/null cell	Nodal Marginal zone	High-grade B cell Burkitt like	Mantle cell
		Burkitt	

MALT, mucosa associated lymphoid tissue; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; LBCL, large B-cell lymphoma. (Adapted from Harris NL et al.¹)

Table 2. Patient characteristics.

		ASCT (n=10)		ASCT + Rituximab (n=11)		Two Tailed
		No.	%	No.	%	P-Value*
Age	Median	56.5		56		0.805
	Range	42-64		40-70		
Gender	Male	7	70	3	27	0.050
	Female	3	30	8	73	
Stage at Diagnosis	I-3	7	18	0	0	0.001
	4	3	29	11	100	
B Symptoms Present	Yes	3	30	4	36	0.757
	No	7	70	7	64	
Histologic Grade Of NHL	Low	4	40	6	55	0.597
	Intermediate	5	50	4	36	
	High	1	10	1	9	
Response Status At Referral	CR I or Rel I	5	50	5	46	0.944
	PR I or Rel 2	2	20	3	27	
	RD or Rel>2	3	30	3	27	
Response Status To Induction	CR	5	50	5	46	0.205
	Very Good PR	2	20	3	27	
	PR	4	40	3	27	
Pre-transplant LDH	Median	223.5		182		0.130
	Range	159-417		145-249		
	Above normal (>214)	6	60	3	27	

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; PR, partial response; Rel, relapse; RD, refractory disease

* Yates corrected chi-square test for 2 by 2 tables and Kruskal-Wallis test for >2 by 2 tables

residual disease such as that attained after high dose therapy followed by autologous stem cell transplantation.

RITUXIMAB AND TRANSPLANTATION

The use of **autologous stem cell transplantation (ASCT)** as a curative approach for the treatment of relapsed or poorly responsive NHL is debated, but many studies provide convincing data to support ASCT for NHL. Despite many successes, relapse, which may be viewed as failure to eliminate **minimal residual disease (MRD)** in the patient by high dose chemotherapy given prior to ASCT, is all too frequent and often occurs in areas of former bulk disease. Studies using gene marking techniques have demonstrated that the autologous bone marrow graft itself may participate in relapse.^{8,9} Despite

reducing the level of contaminating tumor cells, in vitro "purging" of the stem cell graft is unable to eliminate all contaminating malignant cells, leaving a small number in the purged graft.¹⁰ Thus, the post transplant patient should be considered likely to have not only persistent MRD but engrafted tumor cells as well. Hence, the full eradication of lymphoma cells can only be achieved using a "consolidation" approach after ASCT. Unfortunately, at this time in the patients' treatment, additional chemotherapy is toxic and, to a minor extent, might increase the risk of secondary malignancies. Many groups have used anti-CD20 to perform an in vivo purging of the graft just before collection and high dose therapy followed by **autologous stem cell reinfusion (ASCR)**.

At the Roger Williams Medical

Center, a similar approach was studied using rituximab in the setting of MRD. Due to the concern of increasing infectious complications by using rituximab before transplant we chose a consolidation approach. We hypothesized that immune consolidation given immediately after ASCT would improve the outcome of NHL patients because it would treat MRD due to both disease remaining in the patient after high dose chemotherapy as well as tumor cells contaminating the graft. We began a pilot, phase II study of ASCT for NHL with immune consolidation using rituximab. The results were compared to our most recent historical controls receiving the same treatment through ASCT.

Between November 1994 and September 2001, 21 consecutive patients received an ASCT for advanced or relapsed

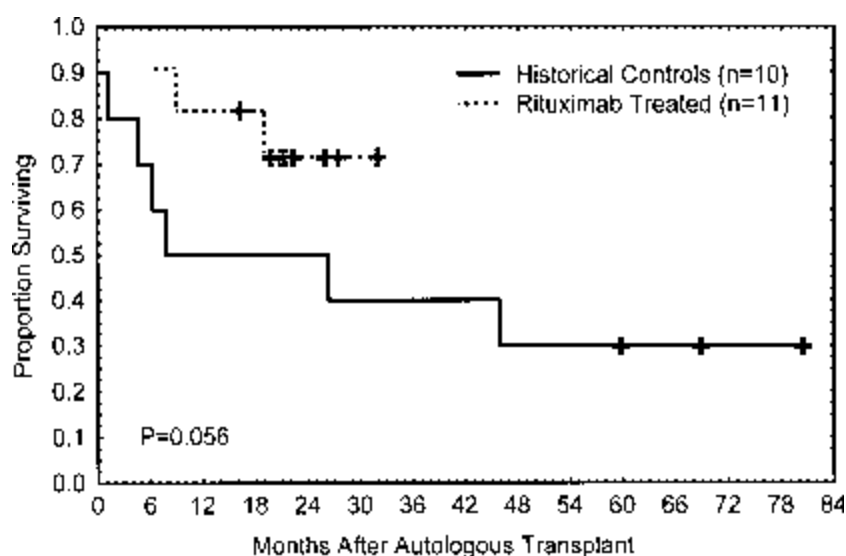


Figure 2. Overall Survival

NHL. The first 10 patients received a standard ASCT; the later 11 received rituximab consolidation following ASCT. (Table 2) The high dose chemotherapy used prior to autologous blood stem cell infusion was CTCb¹¹ consisting of cyclophosphamide (6000 mg/m² total dose), thioTEPA (500mg/m² total dose) and carboplatin (800 mg/m² total dose) chosen for its relatively decreased toxicity compared to other transplant regimens¹² and its known activity in a broad range of lymphomas.¹³ In the consolidation group, all patients were given rituximab starting during the second or third month after transplant at a dose of 375 mg/m² weekly for four weeks, given every six months for five cycles.

The frequencies of serious or life-threatening toxicity during the early post transplant period (days 0 to 100) were similar in both treatment groups. Rituximab was well tolerated with minimal side effects. One rituximab patient presented with a *C. albicans* pneumonia (confirmed by open lung biopsy) 14 months post-transplant but was effectively treated with a long course of fluconazole. The patient remains in complete remission at 32 months of follow-up.

Analysis of **freedom from relapse (FFR)** to estimate the relapse rate was performed at a median follow-up of 24 months with a minimum follow-up of 16 months. The actuarial 30-month relapse rate was 28% for the consolidation group

and 50% for the controls. Overall, 4 relapses were registered in the treatment group and 6 relapses in the control group. The potential advantage observed for the consolidation group was not mathematically significant (two tailed P=0.17) with this small sample size and short follow-up. However, the median time to relapse was 7 months for the historical group and 31 months for the consolidation group.

At the time of this analysis, 10 patients have died, 3 in the consolidation group and 7 in the control group. Four deaths were due to antibiotic resistant opportunistic infections (2), toxicity (mucositis and respiratory failure; 1), or intercurrent events (sudden death at home; 1). Six deaths were due to recurrent disease. The actuarial **overall survival (OS)** rate at 30 months was 70% and 40% for the consolidation and control groups, respectively (two tailed P=0.056. (Figure 2) The data are suggestive of an advantage for the rituximab treated group. Further, the median time to death was 8 months for the historical controls but not yet reached for the consolidated group.

The analysis of **event free survival (EFS)** confirmed an advantage for the consolidation group over the controls. The projected EFS rate at 30 months was 63% and 30%, respectively (two tailed P=0.056). Further, the median time to relapse or death was 4 months for the historical controls and 31 months for the consolidated group. In both the consolidation and control groups, one patient

Table 3. Anti-CD 20 and anti-CD 52 therapeutic antibodies

	Rituximab	Campath-1H
Target antigen	CD 20	CD52
Antigen expression	B cells	B and T cells
Mechanism of action	ADCC*, CDC**, DA***	ADCC, CDC
Dosage	375 mg/m ² i.v./week for 8 weeks	30 mg i.v. three times/week for 12 weeks
Toxicity	Infusion-related	Infusion-related*** Myelosuppression Opportunistic infections
Refractory indolent NHL response rate	48% overall response 6% complete response	14% overall response
Refractory CLL response rate	13% overall response	33% overall response 2-5% complete response

*ADCC antibody-dependent cellular cytotoxicity. **CDC complement-dependent cytotoxicity. ***DA: direct induction of apoptosis.

***Infusion-related side effects: fever, chills, nausea, dyspnea, rash, cough, bronchospasm.

each is alive but in relapse.

These results support the hypothesis that minimal residual disease persisting after high dose chemotherapy and autologous stem cell infusion may be controlled by immunotherapy with rituximab for NHL. It is feasible, non-toxic and appears to provide a major advantage compared to non-consolidated historical controls. Other investigators are exploring the use of rituximab peri-transplant as well.^{14-17,19} We cannot assess the long-term risk of secondary malignancies due to rituximab in these studies.

EMERGING THERAPEUTIC TOOLS Alemtuzumab:

Alemtuzumab (CAMPATH-1H) is a humanized monoclonal antibody targeting CD52, a surface antigen present on most normal and malignant T and B-cells with a high level of expression. Alemtuzumab has been studied in relapsed or refractory B-CLL^{18,19} in T-cell prolymphocytic leukemia and cutaneous T-cell lymphomas²⁰ with reasonable success. The effect on relapsed indolent NHL has been disappointing.²¹ Table 3 compares and summarizes the information known on rituximab and alemtuzumab.

Anti-CD22 and anti-HLA-DR:

Based on the success of the monoclonal antibody approach, new targets are currently in development. Epratuzumab is a monoclonal antibody against the CD22 antigen present on 75% of B-lymphocytes and has been used in phase II clinical trials with a 20-40% overall response rate. In combination with rituximab, the response rate was 67%.²² Another target is HLA-DR expressed on normal and malignant B cells. Apolizumab (Hu1d10) is a monoclonal antibody directed against HLA-DR inducing in vitro lysis of lymphoma cell lines. Although preliminary, a phase one trial showed some durable responses in follicular lymphoma patients.

Radioimmunotherapy:

Indolent lymphomas are highly radiosensitive. Radioconjugated monoclonal antibodies against CD20 have the advantages of acting on CD20 negative malignant neighbouring cells, in poorly vascularized tissue. Zevalin®, a murine

We hypothesized that immune consolidation given immediately after ASCT would improve the outcome of NHL patients because it would treat MRD due to both diseases remaining in the patient after high dose chemotherapy as well as tumor cells contaminating the graft.



anti-CD²⁰ (ibritumomab) conjugated with yttrium 90 is a high energy pure β -emitter and can be administered on an outpatient basis. In a phase III trial, the overall response for the radioimmunoconjugate was 80% versus 44% for rituximab.²³ Bexxar® (tositumomab) is an anti-CD20 monoclonal antibody of murine origin linked with iodine¹³¹ which requires a prolonged stay in a specialised inpatient setting but yields a high rate of prolonged complete remissions in pretreated NHL patients.²⁴ Bone marrow toxicity is dose limiting for both radioimmunoconjugates. The most ideal setting for radioimmunoconjugates is after conventional therapy and stem cell collection but before high dose therapy as additional cytoreductive therapy pre-transplant.

CONCLUSION

The end of the 20th century was marked by the first therapeutic use of targeted specific immune treatments for management of NHL. These monoclonal antibodies are both safe and much less toxic than chemotherapy. They can be combined with chemotherapy, tagged with radioactive elements, or used in the setting of high dose therapy followed by ASCT. New agents are under evaluation. Unfortunately, these are very expensive.

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The Chronic Leukemias: Current and Novel Therapeutic Approaches

Ritesh Rathore, MD, and Gerald J. Elfenbein, MD

In 2003, an estimated 7,300 new cases of **chronic lymphocytic leukemia** (CLL) and 4,300 new cases of **chronic myeloid leukemia** (CML) will occur in the United States.¹ For 2003, the number of deaths due to CLL and CML are estimated at 4,400 and 1,600, respectively. In Rhode Island, 30-40% of an estimated 100 new cases of leukemia will be chronic leukemias.

CHRONIC MYELOID LEUKEMIA

The **World Health Organization** (WHO) defines CML as "a myeloproliferative disease that originates in an abnormal pluripotential bone marrow stem cell and is consistently associated with the **Philadelphia (Ph)** chromosome and/or the *bcr-abl* fusion gene". The hallmark of this disease is the 9:22 translocation, which results from the *bcr* gene (on chromosome 22) being juxtaposed to the *abl* gene (on chromosome 9). The *bcr-abl* oncogene product is a 240 kD protein, which is a constitutively active tyrosine kinase and is a causative factor. Most patients present in the chronic phase of the disease but later develop an accelerated phase or go directly into a blast crisis, a phase similar to acute leukemia. Average survival in chronic phase disease is approximately 5 years and less than a year in accelerated phase or blast crisis.

TRADITIONAL TREATMENT APPROACHES

Interferon alpha

Until recently, **interferon (IFN)**-based therapy has been a first-line option for newly diagnosed patients in chronic phase CML. Approximately 50-80% of patients experience hematologic responses (improvement in blood counts and appearance of the bone marrow). Major (reduction to fewer than 50% Philadelphia (Ph⁺) chromosome positive metaphases in the marrow) and complete (no evidence of Ph⁺ chromosome in the marrow) cytogenetic response rates are 10-40% and 5-25%, respectively. Lack of major hematologic responses after 3 months or major cytogenetic responses after 9-12

months should prompt alternative therapeutic approaches. IFN α_{2b} is given as a single-agent or in combination with cytarabine (Ara-C). Two randomized trials comparing IFN with IFN plus Ara-C showed higher hematologic and cytogenetic responses with combination therapy and also increased survival in one trial. Median survival with IFN-based therapy is 6-7 years and high long-term survival rates (> 10 years) are seen in patients with complete cytogenetic responses.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation (SCT) is the only curative option for CML. Long term remission is believed to be mainly due to the immunologic '**graft versus leukemia**' (GVL) effect that is successful in controlling or eliminating minimal residual disease obtained after high dose chemotherapy. Widespread applicability is limited by donor availability, patient age and general health, and major acute and chronic toxicities. Outcomes are better for patients undergoing transplantation early in the course of their disease, with 5-year survival rates of 75%, 40%, and 10% for chronic, accelerated and blast crisis phases, respectively. The consensus after meta-analysis is that there is no major difference in major transplant associated outcomes between chemotherapy-only preparative regimens and **total body irradiation (TBI)**-containing regimens. The use of improved anti-infective therapy (antifungal and anti-cytomegaloviral) has contributed to improved survival of chronic phase patients. Younger patient age at transplantation and a shorter time from diagnosis to transplantation are associated with superior outcomes.

The lack of matched related donors can be obviated with **matched-unrelated donor (MUD)** transplants. However, lack of available donors, especially in the minority populations and increased toxicity of this approach, mostly due to **graft versus host disease (GVHD)**, remain problematic issues. Outcomes in younger patients with chronic-phase CML under-

going MUD-transplants approach those undergoing related donor transplants.

Autologous Stem Cell Transplantation

Autografting is useful in the setting of patients with incomplete responses to frontline therapy and who lack matched donors. The curative potential is limited by lack of the immunologic GVL effect and the potential contamination of autograft with residual CML cells. As in allogeneic transplants, success is heavily dependent on phase of disease and in a multicenter review, the 3-year survival rates for patients transplanted in chronic, accelerated and blast crisis phase were 60%, 30%, and 0%, respectively. Recent data indicate better survival in chronic phase patients but few patients enter complete cytogenetic remission with this approach. It is unclear presently whether purging (depletion of tumor cells) from the autologous stem cell graft is beneficial or necessary in this setting. One method of prolonging remission status involves the use of post-transplant consolidation using specific immunologic therapies such as interleukin 2 (IL-2) or IFN.

RECENT TREATMENT ADVANCES

Imatinib Mesylate (GleevecTM).

Imatinib mesylate is a small molecule targeted to disrupt *bcr-abl* function and works by preventing phosphorylation of the tyrosine kinase residue. In phase II studies, imatinib was shown to have major responses in all phases of CML. Results of an 1100-patient randomized trial comparing imatinib to IFN plus Ara-C showed that major and complete cytogenetic responses at 12 months were 83% and 68% with imatinib versus 29% and 7% with IFN plus Ara-C ($p=0.001$).² Similarly, one-year progression free survival rates were 97% and 80% for imatinib and combination therapy, respectively ($p=0.001$). Based on these results, the FDA has approved imatinib for first-line therapy in chronic phase CML. Higher doses of imatinib (up to 800 mg/day) may be associated with improvements in responses, especially in pa-

Table 1. New Therapeutic Options

CML
Imatinib mesylate
Reduced Dose Intensity (Mini) transplantation
CLL
Alemtuzumab
Rituximab
Reduced Dose Intensity (Mini) transplantation

tients who have less than a complete response at standard doses of 400 mg/day. Major and complete cytogenetic response rates in patients with accelerated phase CML were 24% and 17%, respectively and were 16% and 7%, respectively in blast crisis patients.

The toxicity profile of imatinib is favorable and commonly includes mild to moderate fluid retention, nausea, muscle cramps, rashes, fatigue and diarrhea. Myelosuppression is more commonly seen with accelerated or blast crisis cases. The significantly lower disease progression seen with imatinib (1.5% vs. 7% for IFN plus Ara-C) may translate into a survival benefit with longer follow up. Impressive cytogenetic responses in all phases of CML, lack of major toxicities and easy oral administration make imatinib the treatment of choice in most settings. There has been a reduction of upfront allogeneic SCT even though the durability of cytogenetic responses with imatinib is unclear at present. Moreover, the frequency and persistence of molecular (*bcr-abl* negative) complete remissions is unknown. Currently, studies are examining the role of imatinib use in combination with IFN and Ara-C. Imatinib is also being incorporated in transplantation strategies.

Reduced Dose Intensity Transplantation

Reduced dose intensity conditioning regimens ('mini-transplants') are less myeloablative in nature and obviate the acute toxicities associated with high dose chemotherapy and standard doses of TBI. Originally targeted for elderly and organ function-compromised patients, this approach has demonstrated major responses in a variety of hematologic malignancies, including CML. In a recent review of seven reports in CML, actual 1-year survival rates of 65-83% were seen in a heavily pre-treated patient population.³ The major anti-leukemia effect stems

from the GVL phenomenon. This approach also utilizes donor lymphocyte infusions in order to induce full chimerism in the recipient and maximize the GVL effect. It is possible that somewhat more

myelosuppressive regimens may add to the efficacy of the GVL effect and result in improved outcomes by providing more disease debulking. Though acute toxicities are lower, major GVHD seems to be no less common or problematic than with standard transplantation.

CHRONIC LYMPHOCYTIC LEUKEMIA

CLL is an accumulative disorder of malignant small B lymphocytes commonly seen in the elderly. As the disorder advances, there is increasing immune impairment, including hypogammaglobulinemia and T cell abnormalities. The increased WBC count is reflective of the impaired apoptosis of CLL cells. This is the commonest leukemia among Caucasians. Staging of CLL identifies risk groups. The median survival from diagnosis for early (stages 0 and I), intermediate (stage II), and advanced disease (stages III and IV) patients is approximately 10 years, 7 years and 1-2 years, respectively. Early stage patients are usually asymptomatic and treatment is offered in the setting of advanced or bulky disease and rapidly progressive or symptomatic early disease stages.

TRADITIONAL TREATMENT APPROACHES

Alkylating Agents

Alkylating agents such as cyclophosphamide or chlorambucil, often in combination with corticosteroids, have been traditionally used in frontline CLL therapy. Comparisons have been conducted for the use of single agent chlorambucil versus combination chemotherapy regimens such as CVP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Even though response rates were higher with combination regimens, a survival advantage could not be demonstrated. Initiation of treatment in early stage CLL has

not proven to confer survival benefit when compared to delayed treatment initiated upon disease progression to advanced stages. Thus, multiagent chemotherapy is not usually offered to patients in general practice.

Purine Analogs

The advent of the purine analogs (fludarabine and cladribine) increased the therapeutic options for this disease in the 1980s. Initial studies demonstrated that these agents were active as salvage therapy in patients previously treated with alkylating agents. Response rates for fludarabine and cladribine as second line therapy were in the range of 30-50% with more complete responses seen with fludarabine. Fludarabine as first-line therapy has shown response rates of 75-80% with a 25-30% complete response rate. The North American Intergroup randomized trial showed complete response rates of 20% and 4% and overall response rates of 70% and 43%, respectively, for fludarabine and chlorambucil. Time to disease progression was superior with fludarabine but no survival advantage was seen. Other studies have examined fludarabine in comparison to regimens such as CHOP or CAP (cyclophosphamide, doxorubicin, prednisone); all of them showed no significant survival advantage with combination chemotherapy. Recent attempts to combine fludarabine with cyclophosphamide have resulted in superior response rates without survival benefits. The Food and Drug Administration (FDA) has approved single agent fludarabine as first line therapy for CLL.

RECENT TREATMENT ADVANCES

Monoclonal Antibodies

Most of the recent advances are in the development of monoclonal antibodies directed against lymphocyte cell surface antigens. Alemtuzumab (CAMPATH-1H™) is a chimeric humanized murine antibody directed against the CD52 antigen, which is present in high density on B and T lymphocytes in CLL. In refractory patients who have failed alkylators and fludarabine, the response rate with alemtuzumab was 33%, with median survival of 16 months for all patients and 32 months for responding patients.⁴ An increased incidence of

severe infections, especially **cytomegalovirus (CMV)** reactivation and **Pneumocystis carinii pneumonia (PCP)** was seen in 27% patients. Prophylaxis for PCP is recommended with early treatment for CMV with ganciclovir or foscarnet upon suspicion of reactivation.

Rituximab (RituxanTM) is a chimeric humanized murine antibody directed against the CD20 antigen, which is present in lower density on B lymphocytes in CLL as compared to lymphoma. As a result, traditional dosing of rituximab has resulted in low response rates. Thrice weekly dosing or high-dose scheduling of this agent obtains more impressive response rates in the 40-50% range.^{5,6} Recent data indicate that concurrent use of combination fludarabine and rituximab⁷ or **fludarabine, cyclophosphamide, rituximab (FCR)** are associated with complete response rates over 50% and overall responses in the 80-90% range. Both these novel therapies hold the promise of improving the outcome for CLL patients, especially when used in combination regimens.

Stem Cell Transplantation.

Allogeneic SCT approaches in CLL have been limited mostly by the elderly patient population and high mortality rates. Allogeneic SCT is an option for young patients (< 50 years) with HLA-matched donors who have high-risk and advanced disease. The favorable GVL effect makes this procedure potentially curative. High complete response rates with a long-term survival fraction of approximately 50% can be expected.⁸ Reduced dose intensity SCT is being evaluated with a view to expand the eligibility pool to safely include elderly patients. Reports indicate high response rates in the 50-60% range in previously heavily pre-treated patients with survival rates comparing favorably to allogeneic SCT.

Difficulty in obtaining sufficiently cleared blood or bone marrow for harvesting stem cells for autologous SCT has been an issue that is likely to recede with the impressive marrow clearance rates obtained with the use of monoclonal antibody and fludarabine combinations. In a recent review,⁸ 4-year disease free survival rates over 65% were reported. Autografting is non-curative in CLL as evidenced by late relapses even after 5 years post transplant.

NEW TRANSPLANT APPROACHES

The Blood and Marrow Transplant Program at the Roger Williams Medical Center has initiated several novel protocols for patients with CLL and CML. In chronic phase CML, patients < 70 years old, without HLA-matched donors, and who have received 12 months of frontline imatinib therapy with lack of complete cytogenetic response, undergo autologous SCT for maximum cytoreduction followed by maintenance imatinib therapy for minimal residual disease. So far, one patient has been treated with this approach and this patient remains in molecular remission 1 year after autologous SCT. In another approach, patients with relapsed CML after therapy (including autologous SCT) receive reduced dose intensity SCT with low dose total body irradiation using HLA-matched or HLA-half matched donors to induce a favorable GVL effect.

In high-risk, relapsed or refractory CLL patients (< 70 years old), *in vivo* purging with alemtuzumab is followed by autologous SCT. Maintenance rituximab is given every six months for 5 cycles as post-transplant immunologic consolidation with the intent of eradicating minimal residual disease. The more typical, elderly patient with failure of prior treatment is eligible for the reduced dose intensity SCT protocol with low dose TBI using matched or half-matched donors to induce a favorable GVL effect. So far, one patient has been treated with this approach. This patient was cytoreduced with alemtuzumab, achieved a complete hematologic remission after autologous SCT, and has just completed rituximab immunoconsolidation. Cytogenetics on marrow are pending.

SUMMARY

Recent developments with targeted therapies have expanded the therapeutic armamentarium (Table 1) for patients with both CLL and CML. Significant advances in allogeneic and autologous donor transplantation have increased the patient eligibility pool and reduced the toxicities while improving upon long term survival results.

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The Latest Treatment Advances for Acute Myelogenous Leukemia

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Acute leukemia is a stem cell disease that usually falls into two subtypes, myeloid or lymphoid. A total of 11,000 new cases of acute leukemia are diagnosed per year in the United States. Overall, acute leukemia is diagnosed in approximately 5 per 100,000 people each year. The incidence of **acute myeloid leukemia (AML)** is 3.6 per 100,000 people with the remainder having **acute lymphoid leukemia (ALL)**.¹ The median age of patients developing ALL is 4 years old, contrasted with 65 years for AML. The incidence of AML rises from 1.8 per 100,000 individuals below age 65 to 16.3 per 100,000 individuals at age 65 and over. This fact highlights the problem in treating patients with AML; most are too old for aggressive, potentially curative therapy such as a standard bone marrow transplant using a matched sibling or unrelated donor. Untreated, 95% of patients with acute leukemia will die within one year of diagnosis. Because the vast majority of acute leukemias are myeloid, we will focus on AML.

ACUTE MYELOID LEUKEMIA: CLASSIFICATION AND ETIOLOGY

New treatment strategies for AML have been, and continue to be, developed as a consequence of advances in the understanding of both cytogenetic and molecular pathogenesis. These new treatments have significantly improved the survival rate. Before 1970, the 5 year survival rate for AML was less than 15%; the current 5 year survival rate is about 40%. In older adults (>65 years of age), however, the 5 year survival rates are less than 10%.²

Eighty to 100% of newly diagnosed patients with AML have a chromosomal abnormality in myeloid cells.³ Most cases of AML are the result of genetic mutations that occur in hematopoietic progenitor cells and the majority of these mutations are acquired rather than inherited. The current **French-American-British (FAB)** classification of AML types M1 through M3 depends upon the vary-

ing degrees of granulocytic differentiation and maturation. Monocytic and granulocytic differentiation defects characterize AML-M4, whereas monocyte differentiation is the predominant feature of AML-M5. AML-M6 is characterized by erythroid morphology and AML-M7 by megakaryocytic features.

A recent retrospective analysis of nearly 2,000 patients has shown that the 5-year survival is directly related to the cytogenetic status of the hematopoietic cells at presentation.⁴ Patients with normal cytogenetics or with favorable cytogenetic abnormalities, such as t(8;21), t(15;17), and t(16;16), have better prognoses. Patients with deletions in the long arm of chromosome 7 and chromosome 5, deletions or inversions of chromosome 3, t(6;9), and the Philadelphia chromosome t(9;22), as well as abnormalities of chromosome 11q23, have relatively poor prognoses.⁵ Genetic deletions seem to be more characteristic of older AML patients, with 5q and 7q deletions found in approximately 17% of patients in this age group. In general, patients with AML whose cells have translocations seem to fare better than those whose cells have deletions. The poor prognosis associated with increased age may be related to the higher incidence of genetic deletions.

In AML, genes located at translocation breakpoints are typically responsible for cellular transcription and transduction of growth signals. Most translocations in *de novo* AML result in a fusion of the affected genes, with production of hybrid proteins. The (15;17) translocation found in most promyelocytic leukemia (PML, M3) illustrates this mechanism where the **promyelocytic leukemia (PML)** gene on chromosome 15 is fused to the **retinoic acid receptor (RAR)** alpha gene on chromosome 17, leading to production of a nonfunctional RAR that does not respond to normal physiologic levels of circulating retinoic acid. Cell transcription and differentiation is thus arrested by the inability of the RAR to activate normal target genes.

The PML gene seems to function as a histone deacetylase, which also serves to suppress gene transcription and cellular maturation. The administration of **all-trans-retinoic acid (ATRA)** allows the histone deacetylation complex to dissociate from the RAR-PML fusion protein, enabling the RAR to function appropriately, which, in turn, leads to cellular differentiation.

Another well-characterized gene rearrangement in AML involves the transcription factor complex **core-binding factor (CBF)**. CBF is composed of an alpha subunit that directly contacts DNA and a CBF-beta subunit that facilitates binding of AML1 to DNA. Three genes (AML1, AML2, and AML3) encode the alpha subunit. It is thought that translocations involving the CBF result in the loss of normal CBF properties, converting CBF from transcriptional activator to inhibitor, thus leading to suppression of transcription of several target genes, including genes for interleukin-3 myeloperoxidase, **granulocyte-macrophage colony-stimulating factor (GM-CSF)**, and the T-cell receptor beta.⁶

The (8;21) translocation, seen in approximately 46% of AML-M2 patients, results in the production of a fusion protein known as ETO/AML, of which the ETO portion from chromosome 8 is involved in histone deacetylation.⁷ This, in turn, serves to block activation of AML1 gene expression, resulting in lack of IL-3 and GM-CSF receptor activation and loss of cellular differentiation/maturation. Inv(16), found in AML-M4 with eosinophilia, is associated with fusion of CBFb to the smooth muscle myosin heavy chain (MYH11) gene. This CBFb-MYH11 chimeric protein directly represses AML1-mediated transcriptional activity by forming inactive complexes in the cellular cytoplasm.⁸

Chemotherapy-related AML, especially following use of topoisomerase II inhibitors, seems to involve translocations at locus 11q23 (the MLL gene). A site within the MLL breakpoint clus-

ter region has been identified as being prone to double-stranded DNA breaks as a result of exposure to topoisomerase II inhibition.^{9,10} To date, at least 38 different translocations have been identified that involve the MLL gene, but the mechanisms of action have yet to be worked out.

TRADITIONAL CHEMOTHERAPY FOR NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

The treatment of AML has involved the administration of intensive combination chemotherapy with an anthracycline (i.e., **daunorubicin (Dnr)**) and **cytarabine arabinoside (Ara-C)**. Treatment hasn't changed since the late 1960s. Dnr and Ara-C have produced long-term survival in about 15% of those patients achieving complete remission.¹¹

In general, treatment for AML consists of an induction phase (e.g., Dnr and Ara-C) followed by a post-remission consolidation phase. The necessity for consolidation treatment was demonstrated in a randomized study in which patients who were treated with induction therapy alone experienced a higher rate of relapse following a shorter period of remission.¹² Subsequent clinical investigation demonstrated that consolidation is essential, whether treatment is given immediately following remission or delayed for several months.¹³

A retrospective review of patients treated with induction Dnr and Ara-C in 5 clinical trials conducted between 1976 and 1994 showed a complete remission rate of 62%, but 76% of these patients relapsed or died.¹⁴ Overall survival at 5 years was 15%, ranging between 9% and 33% for patients less than 55 years old, and between 6% and 15% for patients 55 years old and older. Both disease-free and overall survival was better in younger patients, when more intensive post-remission treatments were employed.

NEWER INDUCTION CHEMOTHERAPY APPROACHES IN AML

Histone acetylation plays a significant role in cellular transcription and leukemogenesis. Histone acetylation allows for greater exposure of DNA to transcription factors by enabling DNA/histone contacts to loosen or relax, thus promoting gene expression and cellular differ-

entiation. Conversely, histone deacetylation is expected to inhibit gene expression and arrest cellular differentiation. The fusion genes PML-RAR and AML-1/ETO have already been described as promoting histone deacetylation. Thus, histone acetylation promoters and **histone deacetylation (HDAC)** inhibitors are logical agents for clinical study in AML. Several HDAC inhibitors are currently under clinical investigation. These include depsipeptide, sodium butyrate, and retinoic acid. Phase 1 trials showed minimal histone deacetylation activity *in vitro* with the use of maximally tolerated doses of sodium phenylbutyrate, precluding further single-agent studies. In one effort to overcome this obstacle, retinoic acid and sodium phenylbutyrate were combined. As a result, significant cellular differentiation was achieved, prompting further clinical investigation.¹⁵

Angiogenesis seems to play a role in leukemogenesis. Overexpression of fibroblast growth factor and vascular endothelial growth factor has been demonstrated in lymphoid and myeloid leukemia, respectively.^{16,17} There are a number of potential targets for angiogenic inhibition, including suppression of angiogenic factor release, binding of the free circulating factor, receptor blockade, or direct interference with endothelial cell function. Clinical trials with thalidomide and the tyrosine kinase inhibitors, SU5416 and SU6668, are in progress.

Using the success of ATRA as a base, investigators have looked at other retinoid compounds for use in leukemia. Fenretinide (N-[4-hydroxyphenyl]retinamide), first developed as a chemopreventive agent,¹⁸ was shown to induce apoptosis in malignant cells whether or not these cells possessed an RAR.¹⁹ Phase 1 testing demonstrated acceptable toxicity, with cases of reversible night blindness being reported.²⁰

Protein kinase C (PKC) activation has been linked with the development of nucleoside analogue resistance. Bryostatins, a PKC inhibitor, has been studied in a number of solid and hematologic malignancies and because of low single agent activity, is currently being testing in combination with cytarabine, fludarabine, and 2-chlorodeoxyadenosine, as well as in

combination with ATRA. UCN-01 (7-hydroxystaurosporine), a selective, but nonspecific, kinase inhibitor with good activity against PKC, has been shown to reverse cytarabine resistance in leukemic cell lines.²¹ Moreover, both bryostatin and UCN-01 have been shown to promote apoptosis via phosphorylation of Bcl-2. Other strategies for overcoming drug resistance are being tested, including reversal of the multi-drug resistance protein gene with quinine and cyclosporine.

POST-REMISSION CHEMOTHERAPY STRATEGIES

The extraordinarily high relapse rate suggests that most patients have residual disease after the completion of induction chemotherapy. Treatment options include consolidation therapy with high dose Ara-C based chemotherapy regimens, high-dose chemo(radio)therapy followed by autologous blood or marrow stem cell support, or high-dose myeloablative therapy followed by **allogeneic blood or marrow transplantation (alloBMT)**. Although the use of protracted "maintenance" therapy following induction and consolidation does not appear, in general, beneficial, some data suggest that maintenance therapy seems to confer disease-free and overall survival advantages, particularly in APL and in older adults with AML.

Most nontransplant consolidation chemotherapy regimens incorporate **high dose Ara-C (HiDAC)**. The mortality rate of giving these treatments is around 10% to 20% per treatment and overall disease-free survival rates ranges from 20% to 50% in several published studies.²²⁻²⁵ Subset analysis indicates that HiDAC was beneficial for patients <60 with favorable prognostic cytogenetics. HiDAC has improved relapse free survival and gave equivalent results to alloBMT in first remission.²⁶

TREATING AML IN OLDER ADULTS

Most patients fall into the unfavorable prognostic risk group since the median age at presentation for AML is 65 years. Older adults also tend to have other co-morbid conditions that make treatment even more difficult. Clearance of cytotoxic drugs may also be impacted by impaired hepatic or renal function. Additional data have disclosed that multi-drug resistance gene overexpression is found in more than 70% of *de novo* AML patients

over the age of 55 years and is highly predictive for failure to achieve complete remission.²⁷ Also, there is a greater incidence of AML arising from prior myelodysplasia, which, in turn, is accompanied by less favorable cytogenetic anomalies. All of these factors contribute to the poor prognosis for AML in older adults.

A large, retrospective review that examined long-term survival among 2882 patients with newly diagnosed AML, treated with various protocols between 1973 and 1996, included 944 patients over the age of 55 years.¹⁴ An update of the long term follow-up data showed that, compared with an overall median survival of 11 months, the median survival in older patients was only 6 months, with a 5-year survival rate of 7.6% (compared with 15% for the entire patient cohort). Another report from a large multicenter randomized trial showed a 9-month median survival and a 5-year survival rate of 8% in patients older than 60 years.²⁸ A third study reported a 5-year survival rate of less than 5% in patients aged over 60 years.²⁹ In older adults high dose consolidation with Ara-C with or without mitoxantrone has not been found to confer any survival benefit.³⁰ Finally, older patients do not benefit by delaying treatment until clinical deterioration occurs.³¹

Monoclonal antibody (MAb) use, although a novel way to treat AML, has a low response rate, has an impressive amount of toxicity and is not curative. Gemtuzumab ozogamicin for example is known for causing liver dysfunction (~20% grade 3-4). Gemtuzumab is composed of an anti-CD33 IgG4 antibody, bound to calicheamicin, an anti-tumor antibiotic toxin that generates double-stranded DNA breaks, resulting in cellular death. Some of other agents include unconjugated anti-CD52, alemtuzumab. Gemtuzumab has been approved by the FDA for relapsed/refractory CD33-positive AML in patients aged 60 years or older who are not considered candidates for other types of cytotoxic chemotherapy.³²

POST-REMISSION BLOOD OR MARROW TRANSPLANTATION

An alloBMT from a **human leukocyte antigen (HLA)** matched sibling can cure 50% to 60% of recipients, even more so than a syngeneic (identical twin) BMT, with less than a 20% risk of re-

lapse following transplantation after first complete remission.³³⁻³⁵ However, the benefits of this treatment are mollified by upfront mortality due to organ damage, immunosuppression increasing susceptibility to opportunistic infections, acute and chronic **graft-vs-host disease (GVHD)**, hepatic veno-occlusive, interstitial pneumonitis, and graft failure. GVHD is responsible for the general restriction of alloBMT to patients younger than 55 years, but GVHD is also responsible for the reduced relapse rate as compared to syngeneic BMT by the **graft-vs-leukemia (GVL)** effect.

*...histone acetylation
promoters and histone
deacetylation (HDAC)
inhibitors are logical agents
for clinical study in AML*



Autologous blood and marrow transplantation (autoBMT), first performed in 1977,³⁶ also allows for the administration of dose-intensive chemotherapy, but, unlike alloBMT, does not help survival with the GVL effect. One reason may be that autoBMT may be associated with reinfusion of leukemic cells. Beginning in 1985, **peripheral blood hematopoietic progenitor cells (PBSC)** were successfully harvested, cryopreserved and later reinfused. PBSC may have a lower tumor burden than marrow.³⁷⁻³⁹ The role of graft purging (depletion) of tumor cells has not yet been proven to have any benefit except in small, single institution studies.⁴⁰ Both PBSC and autoBMT produce disease-free survival rates ranging between 35% and 50% in AML patients after first remission. Treatment-related mortality ranges from 10% to 20%.

Comparison of purged or unpurged autoBMT versus high dose consolidation in patients achieving a first complete remission has yielded equivalent results. In addition, alloBMT and autoBMT after first remission produced equivalent survival. Comparable survival was achieved in the high dose chemotherapy arm when relapsed patients subsequently underwent autoBMT as salvage treatment.⁴¹⁻⁴⁵

RELAPSED AND REFRACTORY AML: NEXT STEPS

For the majority of AML patients treated with chemotherapy alone, disease recurrence remains the major obstacle to overcome. The most important factor is duration of first remission.⁴⁶ Patients whose remission has lasted for 2 years or more before recurrence will achieve a second remission in 50% to 60% of cases, even when the same initial treatment regimen is repeated. When the first remission lasted 12-14 months a 40% chance is found. In patients whose remissions lasted less than 1 year or who failed to achieve a first remission (primary refractory disease), only 10% to 20% ever attained complete remission. Long term survival at 3 years in the longer duration remission group is approximately 20% to 25%, while the shorter duration remission groups have no appreciable survival.⁴⁷ Therefore, treatment decisions must be based, in large part, upon an individual's potential for obtaining and maintaining a second remission. Those patients who are at greater risk for failure should not be offered standard therapies as a matter of course.

Ideally, patients with short duration first remissions, barring other complicating factors, should be considered as candidates for alloBMT and autoBMT, which can achieve approximately 30% long-term survival rates.^{48,49} Survival is similar whether or not chemotherapy precedes transplantation for either type of transplant.^{50,51}

If younger than 55 years with primary refractory disease, alloBMT is superior to autoBMT.^{52,53} Transplant registry data show a leukemia-free survival advantage of 41% for alloBMT vs 17% for autoBMT for patients younger than 30 years old with at least 1 year or more of initial complete remission.⁵⁴ If older than 30 years with less than 1 year of initial complete remission, either transplant modality had a higher 3-year leukemia-free survival compared with chemotherapy (18% vs 7%, respectively).⁵⁵

An investigational new approach is to maximize the GVL effect and to minimize the toxicity to the vital organs from high dose chemotherapy. A single institution study open at Roger Williams Medical Center has already shown exciting results and may hold the key for uni-

versal treatment of relapsed or poor-prognosis AML patients of any age.⁵⁶ While only 35% of patients otherwise eligible for allogeneic, nonmyeloablative, blood or marrow transplantation have an HLA-identical sibling donor, nearly 100% of patients have HLA-haploidentical related donors. Relapsed or refractory patients receive very low dose whole body radiation (100cGy) as conditioning for the graft and then receive a PBSCT containing a precise number of CD3+ cells (T cells). Three of 4 evaluable patients with AML achieved a complete response and one patient who is not yet fully evaluable has achieved a partial response. Of interest, all responses occurred outside of detectable chimerism at 2 weeks after PBSCT (transplanted cells were not detectable). This is an outpatient treatment protocol with well defined toxicities (mainly transient pancytopenia) well tolerated by elderly and infirm patients. This is the first report of successful HLA-haploidentical cellular immunotherapy achieving a complete response for patients with end-stage, refractory hematologic malignancies. Further refinement using interactions between **killer immunoglobulin-like receptors (KIR)** and HLA class I ligands may even enhance success of this treatment.⁵⁷

SUMMARY

The research into pathogenesis and mechanisms behind AML is advancing rapidly, but in general, translation into global application for the majority of patients is wanting. As more becomes known about the cytogenetic and molecular characteristics of leukemia cells and the pathways of leukemogenesis are further elucidated, it is hoped that future therapies will be directed more specifically toward the least toxic method to eradicate clonal malignant cells. HLA-haploidentical and alloBMT using KIR mismatch may dramatically improve survival for many more patients.

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Future Prospects For Patient Care Utilizing Autologous Lymphoid and Hematopoietic Stem Cells

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IMMUNOTHERAPY USING HERCEPTIN®-TARGETED, ACTIVATED AUTOLOGOUS T CELLS

Women with high risk, locally advanced (stage II-III with ≥ 4 positive lymph nodes) breast cancer or metastatic (stage IV) breast cancer, and men with **hormone refractory prostate cancer (HRPC)** could benefit from new approaches to improve lengths of remissions and overall survival, to prolong clinical responses, and to improve quality of life. Even minor responses or relief from bone pain may help those with bone metastases. Many patients with these diseases share an overexpression of *Her2/neu* on their cancer cell membranes. Overexpressed *Her2/neu* is an excellent target for monoclonal antibody therapy with Herceptin® (anti-*Her2/neu*).¹

Immunotherapy with autologous T cells has been studied both *in vitro* and *in vivo* for over 25 years. T cells obtained by leukapheresis can be expanded *ex vivo* and activated with the monoclonal antibody OKT3 (anti-CD3). **Activated T cells (ATC)** are efficient killers of tumor cell lines *in vitro* and show promise *in vivo* in women with stage IV breast cancer (reducing relapse rates) after massive cytoreduction from high dose chemotherapy and stem cell transplantation. *In vitro* studies show that ATC may be made even more efficient killers by “arming” them with a “bispecific” antibody produced by the chemical heteroconjugation of OKT3 (anti-CD3) and Herceptin, (anti-*Her2/neu*) monoclonal antibodies, yielding a product we call Her2Bi.²

When armed with nanogram amounts of Her2Bi, ATC aggregate with *Her2/neu* positive breast and prostate cancer cell lines and are highly cytotoxic to these cell lines at extraordinarily low effector to tumor cell (E:T) target ratios (e.g., 5:1). Armed ATC from 10 normal subjects and 6 cancer patients displayed mean ($\pm$ SD) cytotoxicity $59 \pm 11\%$ and $32 \pm 9\%$, respectively, above that seen for ATC alone

at E:T of 20:1.³ Tumoricidal cytokines (IFN γ , TNF α , and GM-CSF) as well as chemokines (RANTES and MIP-1 α) were secreted when armed ATC bound to tumor targets. Armed ATC were able to kill tumor targets 4 times consecutively and to divide 3 times in 13 days while continuing to bear Her2Bi on their surface.⁴ In SCID/Beige mice, prostate tumors were prevented in 100% of the mice by co-injections of armed ATC with tumor cells. Established prostate tumors could be ablated in 40% of the mice given twice weekly intra-tumoral injections of armed ATC.⁵ These preclinical studies support the rationale for clinical trials.

The FDA has granted us approval to expand anti-CD3 ATC *ex vivo*, to produce the bispecific antibody Her2Bi, and to arm ATC with Her2Bi in order to evaluate a unique non-toxic clinical treatment strategy for diseases that overexpress *Her2/neu*. This approach combines the cytotoxic capacity of ATC with the specific targeting ability of Herceptin antibody to improve tumor lysis. Immunotherapy with ATC armed with Her2Bi is being used to treat patients with breast, prostate, and pancreatic cancer in FDA approved Phase I/II clinical trials (listed at www.cancer.gov/clinical_trials). Phase I studies assess side effects of armed ATC during dose escalation in sequential cohorts of patients. Phase II studies assess clinical response rates of individual diseases to armed ATC.

To date, 5 patients with breast cancer, 4 patients with HRPC, and 1 patient with metastatic pancreatic cancer have been treated at beginning dose levels without any life-threatening reactions. Striking to us at this low dose level is the observation that 4 patients have had more than a 50% reduction in their pain medication requirement. We expect that these studies will provide proof-of-concept that high numbers of Her2Bi armed, activated T cells will provide a valuable anti-tumor effect without undue toxicities to patients.

AUTOLOGOUS ADULT STEM CELLS AND TISSUE REPAIR

Recently, our understanding of adult marrow stem cell biology dramatically changed. Marrow hematopoietic stem cells have the capacity to produce nonhematopoietic cells in diseased or injured tissues. Mice transplanted with lethal genetic tyrosinemia have had massive repopulation of liver cells with purified marrow stem cells and a number have been cured.⁶ In a similar vein, Orlic and coworkers⁷ have studied mice with ischemic cardiac lesions. Such mice were either infused with purified marrow stem cells or had endogenous marrow stem cells mobilized. These stem cell approaches resulted in the production of cardiac myocytes from marrow and a decrease in mortality of the mice. Similar work has shown that marrow cells can produce epithelial cells in lung,⁸ gut, and skin,⁹⁻¹¹ neural cells in brain,¹² bone cells¹³ and skeletal muscle cells.¹⁴ Critical aspects of these studies have been the method of tissue injury and the details of the transplantation. When cardiotoxin has been injected into the anterior tibialis muscle and the muscle has been irradiated, infusing syngeneic marrow cells or mobilizing endogenous stem cells has resulted in very significant conversion of marrow cells to skeletal muscle cells. Similarly, after irradiation and wound production, stem cells produce skin appendages. Not all methods of tissue injury, however, respond to stem cell “therapy.”

These results are now being applied to treatment of human diseases. Marrow cells have been infused after angioplasty in cardiac patients in phase I/II studies in Germany and Italy with promising results as well as safety profile. Studies carried out by Drs. Evangelos Badiavas and Vincent Falanga at **Roger Williams Medical Center (RWMC)** have shown dramatic effects of healing of chronic refractory skin wounds by local application of autologous bone marrow cells.¹⁵ In

these studies, patients with non-healing wounds (over 1 year) had fresh marrow collected and a portion was applied to the skin wound and injected in areas around the wound. The other portion of the marrow sample was cultured *in vitro* and subsequently applied to the wound in a similar manner. Three patients with chronic refractory wounds were treated in this manner, with healing of the wounds in all cases. Although the number of patients treated is small, we believe that this is the first clear-cut demonstration of adult marrow stem cells effectively treating a non-marrow disorder.

There has been a good deal of confusion of the roles of embryonic stem cells and adult marrow stem cells. The former have raised ethical and religious issues since the cells are derived from blastulas from developing embryos. These cells have been studied in mice and man and found to have great potential for indefinite growth in tissue culture and have the ability to produce many different cell types. With the establishment of approaches to culture human embryonic stem cells, many investigators have envisioned great therapeutic potential. Unfortunately, these cells are hard to regulate and, at least in murine transplant systems, ordinarily produce tumors, many of which become malignant. This has not been tested in human transplants. Adult marrow stem cells, on the other hand, have been used for years in marrow transplantation. Their clinical use has been established, as has their safety profile. There is little risk of tumor formation, and with autologous (same person) transplants, virtually no side effects of the marrow infusion. With allogeneic marrow or stem cell transplantation there is the risk of graft-versus-host disease, which has been extensively studied and can be treated. The discovery that adult marrow stem cells can produce cells in a variety of nonhematopoietic organs has opened the possibilities for a variety of therapeutic approaches to replace damaged or diseased tissues. Ischemic cardiac disease, serious lung or liver disease, chronic wounds or burns all may be appropriate candidates for stem cell therapies. Chronic neurologic disorders such as Parkinson's, Alzheimer's disease, and stroke are also candidates for therapy, as

is muscular dystrophy. The critical issues are whether or not enough marrow stem cell to tissue cell conversion could occur to restore organ function. As noted, mouse models have shown that this is possible for both cardiac and liver disease, and our recent wound healing studies indicate that marrow treatment may be effective in human disease. Current studies in the Center for Stem Cell Biology at RWMC are focusing on details that may improve such conversions; these include the number and functional state of the infused cells, additional organ or tissue injuries that may enhance the conversion events and details of the actual transplantation regimens.

The work in the Stem Cell Center at RWMC and the pioneering clinical studies of Drs. Falanga and Badiavas have led to the formation of The Center for Stem Cell Tissue Restoration at RWMC. This Center will focus initially on the treatment of chronic refractory skin wounds in patients with peripheral vascular disease, diabetes, and other chronic diseases. Recent progress in basic work in the Center, showing very high rates of cellular replacement in skeletal muscle and lung tissues, has provided the basis for the development of clinical protocols for the treatment of muscular dystrophy and serious lung disorders. We anticipate that such experimental therapy will become available over the next 1-2 years.

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The Relationship Between Depression and Cancer Survival

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Numerous studies have shown that psychosocial variables are associated with medical outcomes in cancer patients and other patient populations. For example, cancer patients who are married or have other sources of social support have been found to have lower rates of morbidity and/or mortality.^{1,2} Studies with various patient populations have shown a relationship between style of coping and survival, with most studies suggesting that denial is protective.^{3,4} Patients' outlook on their disease (e.g., stoic acceptance versus fighting spirit) has been shown to predict medical outcomes in many though not all studies investigating these factors in patients with cancer.⁵ Psychiatric symptoms and negative mood states (e.g., depression and anxiety) have been associated with less favorable medical outcomes in various patient populations including HIV⁶ and cardiac⁷ patients. In research involving cancer patients, the relationship between emotional distress and medical outcomes has been less clear.

SURVIVAL FOLLOWING CANCER DIAGNOSIS AND TREATMENT

Of twenty-one studies investigating the relationship between depression or related psychological variables and survival in cancer patients (Table 1), the majority of those that included measures of depression found that depression is associated with decreased survival.⁸⁻¹⁵ Three studies failed to find any significant relationship between depression and survival.^{14,15,16} One of the studies that failed to find a significant relationship revealed a trend toward decreased survival¹⁴ and another revealed a trend toward increased survival¹⁵ in cancer patients who scored higher on measures of depression. Moreover, two studies indicated that higher scores on measures of depression were related to increased survival.^{3,16}

Studies of other psychological variables related to depression and survival in cancer patients also have produced inconsistent results. Three studies linked hopelessness and helplessness to decreased survival,^{3,4,17} while one found no signifi-

cant relationship between hopelessness and survival.¹⁸ One study of breast cancer patients linked joy to increased survival.¹⁹

Some of the inconsistency can be attributed to methodological differences. Some studies predicted only group membership (e.g., survivors versus non-survivors; long-term survivors versus short-term survivors) rather than using more powerful survival analyses. Many had small sample sizes or few subjects who were depressed. The researchers employed various instruments to measure depression, some of which can be criticized for being insensitive, nonspecific (e.g., combining depression and anxiety or depression and coping), or susceptible to response bias from self-reports. The timing of the assessments varied: some subjects were as-

sessed shortly after diagnosis; others were assessed much later in treatment. Emotional distress tends to be highest shortly after diagnosis²⁰ and possibly just before bone marrow transplant.²¹ Additionally, key information about the patients often was unreported. For instance, the medical variables in some studies may not have been sensitive enough to capture medical prognostic factors. The studies typically did not report what, if any, psychiatric or psychosocial treatment patients identified as depressed received. If patients received treatment and recovered from depression, this could obscure a relationship between prior depression and later survival. Finally, the patient populations were heterogeneous, and the relationship between depression and survival may differ for patients with different types of cancer.

Table 1.
Title. Studies on the relationship between depression or related variables and survival in cancer patients.

Study	Type of cancer/treatment	n	Psychosocial variable	Relationship with survival
Andrykowski et al. (1994)	Leukemia-BMT	42	Depression Anxiety	None Decreased survival
Brown et al. (2000)	Melanoma	426	Positive mood & lack of concern	Decreased survival
Cassileth et al. (1985; 1988)	Melanoma	359	Hopelessness	None
Celan et al. (1991)	Leukemia-BMT	100	Depression	Decreased survival
Dean & Surtees (1989)	Breast	121	Hopelessness & helplessness Depression & anxiety	Decreased survival Increased survival
Derogatis et al. (1979)	Breast	35	Depression & Anxiety	Increased survival
Edwards et al. (1985)	Testicular	26	Depression & anxiety	None trend toward increased survival
Faller et al. (1997; 1999)	Lung	103	Depression & distress	Decreased survival
Gelhan (1996)	Breast	40	Anxiety & distress	Decreased survival
Janssen et al. (1987)	Breast	49	Various	None
Jensen (1997)	Breast	52	Hopelessness & helplessness	Decreased survival
Leigh et al. (1987)	Various/radiation	101	Depression & anxiety	Decreased survival
Levy (1988)	Breast	36	Joy	Increased survival
Molassiotis et al. (1997)	Various-BMT	31	Hopefulness	Increased survival
Milo (1998)	Various-BMT	200	Depression	Decreased survival
Milo et al. (1998)	Breast-BMT	100	Depression	Decreased survival
Naughton et al. (2002)	Lung	70	Depression	None-trend toward decreased survival
Pettingale et al. (1985)	Breast	57	Hopelessness & helplessness	Decreased survival
Stommel et al. (2002)	Various	871	History of depression	Decreased survival
Tross et al. (1996)	Hepatic	280	Emotional distress	None
Wechs et al. (1998)	Breast	32	Depression & anxiety	Decreased survival

SURVIVAL FOLLOWING BONE MARROW TRANSPLANT FOR LEUKEMIA AND OTHER MALIGNANCIES

Of the 21 studies that investigated the relationship between emotional variables and survival in cancer patients, five involved patients who were treated with bone marrow or stem cell transplant. These studies of patients with leukemia and other malignancies have yielded more consistent results. In 1991, Colon and his colleagues demonstrated that depressed mood prior to undergoing allogeneic bone marrow transplant was associated with shorter survival times following transplant in 100 patients with acute leukemia.⁸ In 1998, a study of 100 breast cancer patients found that depression was associated with shorter survival times following autologous stem cell transplant.²² Specifically, patients with clinically significant elevations on a depression measure prior to transplant had a 49% greater chance of dying within the next two years. A subsequent study of 200 cancer patients undergoing bone marrow or stem cell transplant for various malignancies found that depression was associated with a 25% lower survival rate.²³ Andrykowski and colleagues²⁴ failed to find such a relationship in 42 patients with acute or chronic leukemia who underwent allogeneic bone marrow transplant. However, these authors found that anxious preoccupation was associated with shorter survival times. In another study, decreased hopefulness was found to predict shorter survival times in 31 patients who underwent allogeneic bone marrow transplant.²⁵ Taken together, these studies suggest that there is a significant relationship between emotional distress, especially depression, and survival following bone marrow transplant after controlling for relevant medical factors.

CONCLUSIONS

To date, studies investigating the relationship between emotional distress, particularly depression, and cancer survival have yielded mixed results. The majority supported the conclusion that depression has a negative effect on survival; some studies failed to find a significant relationship; a few found the opposite relationship. The data on patients who underwent bone marrow transplant for leukemia or

stem cell transplant for other malignancies, though sparse, consistently showed that emotional distress (either depression or anxiety) was related to decreased survival.

There are several reasons to suspect that a predictive relationship exists between depression and cancer survival. First, studies of patients with other diseases have demonstrated an association between depression and survival. Second, depression has been shown to affect both immune and endocrine functioning, which in turn, can affect cancer progression.²⁸ Third, depression and anxiety have been shown to affect compliance with medical treatment, though not necessarily in a consistent direction.^{26,27} In the studies reviewed, information regarding the psychosocial treatments provided to patients who were significantly distressed typically was not provided. Thus, it is possible that psychiatric problems that are successfully treated do not affect later survival. Patients who exhibit clinically significant levels of emotional distress after adjusting to the diagnosis cancer should be treated with psychiatric and/or psychological interventions to decrease their symptoms and possibly to extend their survival. Patients with milder symptoms might benefit from support groups or psychotherapy groups designed for cancer patients.²⁹

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Persistent Candidemia in a Leukemic after Allogeneic Transplantation

The patient was a 39 year-old Hispanic male, diagnosed with acute lymphoblastic leukemia (ALL) 3 years prior to bone marrow transplantation (BMT). At presentation, a complete remission was induced and maintained with standard chemotherapy agents. Four months prior to BMT the patient was found to be in first relapse. Two attempts with chemotherapy to reinduce complete remission failed. Each was associated with prolonged periods of aplasia and neutropenic fevers. Despite repeated negative cultures, fevers persisted and amphotericin B was given empirically for presumed systemic fungal infections during each aplasia. As salvage therapy for refractory ALL, the patient received an HLA-identical, allogeneic BMT from one of his sisters after treatment with high dose busulfan and cyclophosphamide. The donor received granulocyte colony-stimulating factor prior to donating her marrow. The patient experienced rapid engraftment and was no longer neutropenic 15 days after BMT. However, he experienced fever during aplasia, which terminated with granulocyte recovery to more than 500/mm³. Prophylaxis for acute graft-versus-host disease involved cyclosporine alone. Beginning on day 19, the patient experienced the first of many complications including Herpes labialis, Acinetobacter and cytomegalovirus pneumonias, Clostridium difficile enteritis, respiratory failure, acute renal failure, and hepatic veno-occlusive disease. A lipid formulation of amphotericin was begun on day 20 for presumed, but not documented, systemic fungal infection for a 10 day course.

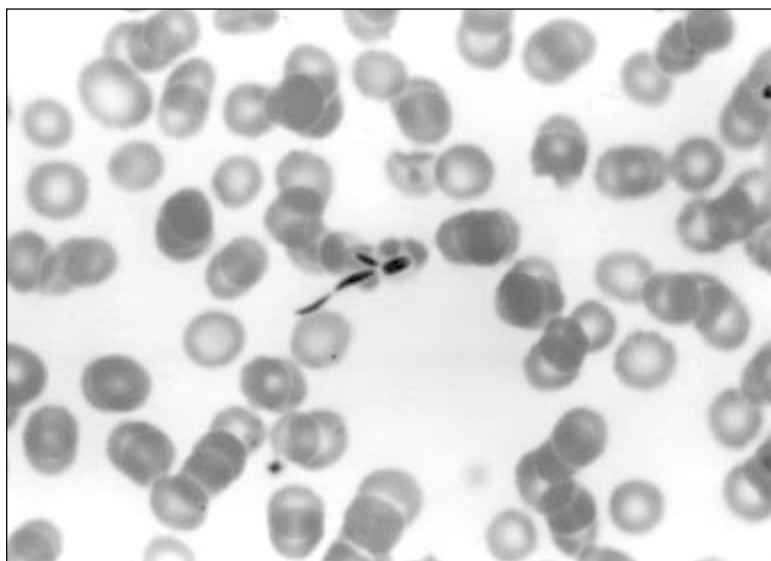


Figure 1. *Candida parapsilosis* on routine evaluation of peripheral blood. Wright-Giemsa, oil immersion x1000. Fungi of any form are extremely rarely seen on examination of blood smears although they may, somewhat more frequently, appear in bone marrow specimens.¹ The presence of yeast forms on smear is indicative of the high fungal load in the patient and is a prognostic sign of very poor outcome despite apparently appropriate antifungal therapy.

On day 35, the patient developed a gastrointestinal hemorrhage with associated hypotension. Blood cultures from that day grew *Candida parapsilosis*. When these cultures were reported out on day 37, the patient was started once again on a lipid formulation of amphotericin, which was dosed based upon recommendations for renal failure. Despite aggressive amphotericin therapy, his blood was never cleared of *C. parapsilosis*. The patient expired on day 44 from amphotericin resistant fungemia in all likelihood related to his central venous catheter that could not be replaced surgically because of persistent thrombocytopenia and refractoriness to platelet transfusions and could not be removed because of the absolute need for venous access.

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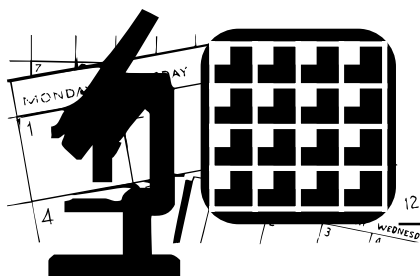
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Neoadjuvant Therapy With High Dose Chemotherapy Via Isolated Pelvic Intra-abdominal Perfusion With Bone Marrow Stem Cell Support For Advanced Endometrial Cancer

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Advanced abdominal and pelvic malignancy represents a major challenge to the surgical oncologist. Usually patients receive palliative surgery or systemic chemotherapy with only minor responses and little or no survival benefit. To optimize the utilization of the chemotherapeutic drugs, alternative approaches have been developed such as regional chemotherapy and high-dose chemotherapy with bone marrow support. The former consists of tumor targeting by direct administration of higher dosages of chemotherapeutic agents into the blood vessels feeding the tumor area. The latter uses systemic myeloablative doses of chemotherapy followed by rescue with either bone marrow or peripheral blood cell precursors (stem cells).

Isolation of the pelvic vasculature to treat pelvic malignancies is a technique that has evolved over the last 40 years. Intra-arterial chemotherapy with nitrogen mustard was initiated in the 1950s. Currently, alkylating agents, such as phenylalanine mustard is used more commonly for intra-arterial chemotherapy regimens. Regional perfusion by extra-corporeal circuit was introduced separately by Creech and Stehlin in the late fifties.¹⁻³ Since that time, approximately 20 studies have described the use of isolated pelvic perfusion in 377 patients of whom 39% had colorectal cancer, 36% had gynecologic malignancy and the remaining few had soft tissue tumors (5%), melanomas (4%), urinary tract cancer (3%) and male genital tract cancer (2%). Isolated pelvic perfusion achieves high drug level in the pelvis (pelvic:systemic ratio of 2.8-13.3:1) by isolating the pelvic vasculature with occlusion of the large abdominal vessels with intra-vascular balloons and external thigh tourniquets.

Our team has utilized the minimally invasive procedure of isolated pelvic perfusion using the balloon occlusion technique both in the palliative and curative setting.^{4,5} While palliative perfusions may ameliorate the quality

of life, the neo-adjuvant approach has the potential of facilitating the effectiveness of a curative resection. Our last report of neo-adjuvant isolated pelvic perfusion included 10 patients with unresectable pelvic colorectal cancer. Almost all patients underwent 2 courses of pelvic perfusion and 8 of them received curative surgery. An R0 resection was possible in 3 of these 8 patients. Overall, 2 patients were alive without disease at 16 and 32 months, one is alive at 12 months with disease, and seven have died of disease 5-20 months thereafter.⁵ Long-term survival has also been achieved for soft tissue tumors and cancer of the cervix.^{6,7}

The current report describes the use of isolated chemotherapeutic perfusion of the pelvis and upper abdomen for advanced recurrent endometrial cancer combined with stem cell support to counteract the myelotoxicity from high-dose chemotherapy administered during the perfusion. The patient was subsequently resected of all disease, and remains with no evidence of disease two and a half years after resection.



Figure 1A. Abdominal CT scan prior to pelvic perfusion revealed multiple masses in the peritoneal cavity including 7 cm mass in the right lower quadrant and a 5 x 14 cm mass along undersurface of transverse colon and invading into the rectus abdominis anteriorly.

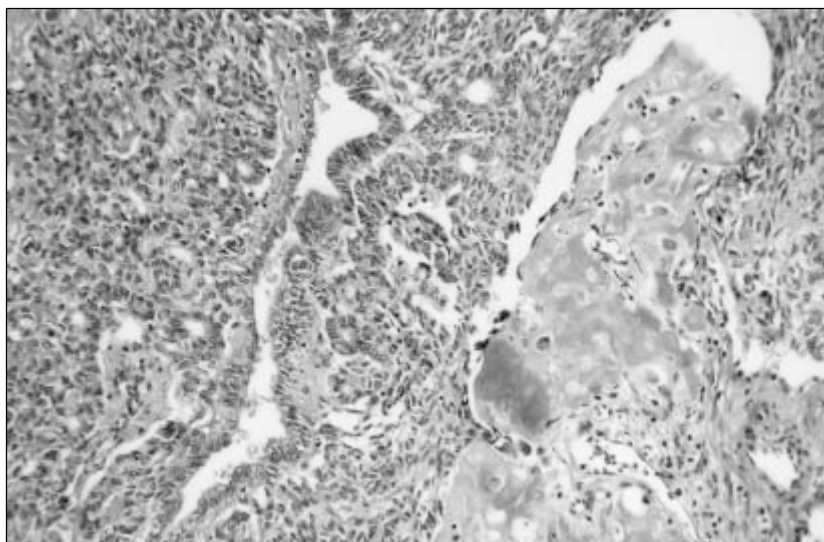


Figure 2A. Endometrial carcinosarcoma prior to pelvic perfusion. The poorly differentiated adenocarcinoma (left) has a cribriform growth pattern with occasional well-formed glands. The heterologous mesenchymal component (right) is composed of interlacing, poorly mineralized bone trabeculae and malignant osteocytes (H&E, 100x magnification).

CASE REPORT

A 70-year-old female with a history of endometrial cancer treated with 500 cGy of radiation and total hysterectomy bilateral salpingo-oophorectomy, remained disease free for 18 years. Two and a half years ago she presented to her primary care physician with a complaint of increased abdominal girth. On physical exam, a mid-abdominal mass was palpated and a **computed tomography (CT)** scan revealed multiple large abdominal masses. Biopsies demonstrated well-differentiated, ER and PR positive, adenocarcinoma consistent with recurrent endometrial carcinoma. The patient began a course of chemotherapy, paclitaxel 175 mg/m² and carboplatin 235 mg/m² every 21 days for three cycles, and presented to our office for options of further treatment modalities.

HISTORY AND PHYSICAL EXAMINATION

Medical history was significant for left upper lobe lung cancer, resected by lobectomy 10 years prior, GERD, peptic ulcer disease, arthritis, hypertension and hypercholesterolemia. Surgical history also included appendectomy, parotid tumor resection, cholecystectomy, knee repair, hysterectomy. Medications included a combination of bisoprolol, hydrochlorothiazide, atorvastatin, lorazepam, and **non-steroidal anti-immune drugs (NSAIDs)** for arthritis. The patient quit smoking 10 years prior. Family history was significant for maternal ovarian cancer. Review of systems was significant for a 15 lb (7 Kg) weight loss over the past six months. Physical exam revealed healthy appearing obese woman in no apparent

distress. Her weight was 191 lb (89 Kg), afebrile with normal vital signs. The abdomen was protuberant and non-tender with a 15 cm mass in the mid-abdomen with some right pelvic fullness. The pelvic exam revealed a foreshortened vaginal cuff and a mass in the anterior pelvic vault that extended to the right side. The rectal exam was guaiac negative with no masses felt in the pouch of Douglas. The rest of the physical exam was unremarkable.

LABORATORY DATA

CT scan of the abdomen, chest and pelvis revealed several hepatic lesions, the largest measuring 3 cm. There were multiple masses in the peritoneal cavity, a 5 x 4 cm mass obstructing the right ureter and ureterovesical junction, a 7 cm mass in the right lower quadrant and

a 5 x 14 cm mass along the undersurface of the transverse colon that was invading into the rectus abdominis anteriorly. Pelvocaliectasis and ureterectasis due to obstructing mass in the pelvis were also noted. (Figure 1A).

CLINICAL COURSE

After she completed three cycles of systemic chemotherapy (paclitaxel/carboplatin), a CT scan showed progression of disease. A cystourethroscopy with right retrograde pyelogram was done and a right ureteral stent was placed to relieve the tumor obstruction. Biopsies of the lesion invading the bladder revealed poorly differentiated adenocarcinoma with squamous and heterologous mesenchymal components consistent with carcinosarcoma. (Figure 2A) The tumor was **estrogen and progesterone receptor (ER/PR)** positive, cytokeratin (CK-7) positive and CK-20 negative.



Figure 1B. Abdominal CT scan after pelvic perfusion revealed a large heterogeneous mesenteric mass in the anterior abdomen to the left of the midline consistent with metastatic disease measuring 3.5 x 9 cm.

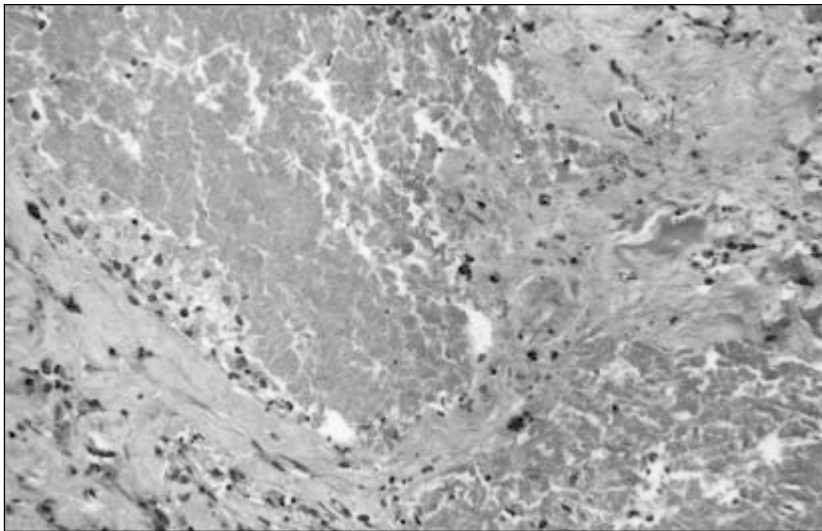


Figure 2B. Endometrial carcinosarcoma after pelvic perfusion. Representative section of the omental tumor showing necrosis, hemosiderin-laden macrophages and hyaline fibrosis (H&E, 200x magnification)

Bone marrow was harvested from the patient immediately prior to high dose neoadjuvant pelvic chemotherapy using isolated pelvic perfusion with balloon occlusion technique and extra corporeal bypass (110 mg/m² l-phenylalanine mustard and 44 mg/m² paclitaxel in four divided doses over 60 minutes). During the initial 5 minutes of the procedure, a portion of the total drug dose was given with the occlusive balloons above the renal artery branches. The remainder of the drug dose was given with the balloons below the renal artery branches, protecting the kidneys from the chemotherapy and isolating the infra-renal and pelvic viscera. A left groin node taken at this time was negative for neoplasm. The patient received the rescue autologous bone marrow transplant one day following the chemotherapy procedure. She tolerated the procedure well with estimated blood loss of 300 – 400 cc but had a prolonged hospital stay (61 days) due to prolonged neutropenia and mental status changes attributed to high dose chemotherapy.

The CT scan obtained after pelvic perfusion showed a questionable 1 cm low attenuation hepatic mass. There was also a 3.5 x 9 cm heterogeneous mass that extended below the level of the iliac crest. Bilateral hydronephrosis was also noted. (Figure 1B)

Two months after pelvic perfusion, an exploratory laparotomy with lysis of adhesions and resection of intra-abdominal metastasis, transverse colon, ileum, cecum and omentum was done. Two tissue expanders were placed in anticipation of radiation therapy. The multiple specimens included a mass invading the transverse colon with attached omental carcinomatosis, one invading the right ureter, one with retro-peritoneal and peri-ureteral extension and one with right iliac side wall invasion. Pathological examination of the surgical specimen revealed poorly differentiated endome-

To our knowledge, our patient is the first reported case in whom high-dose chemotherapy was delivered with isolated pelvic perfusion and bone marrow rescue for advanced gynecologic malignancy.



metastatic endometrial carcinoma.

DISCUSSION

The technique of isolated chemotherapeutic perfusion for pelvic and intra abdominal malignancy provides high dose intravascular chemotherapy to the affected viscera as demonstrated by this patient. This technique preferentially delivers higher doses of chemotherapy to the abdomen and pelvis than can be delivered through systemic therapy. The intra-arterial and venous balloon occlusion technique via groin vessels is a low risk/low morbidity operative technique that can be repeated in each groin if necessary. Although this patient did not receive the planned second pelvic perfusions because of the severe marrow toxicity from the first perfusion, the high level of clinical response (shown by CT scan) to the initial perfusion permitted subsequent curative resection via laparotomy. The optimum number of high dose chemotherapy perfusions needs to be defined in a prospective phase II clinical study. It may be beneficial to complete two perfusions within 3 weeks to achieve very high

trial adenocarcinoma with focal elements of carcinosarcoma in the omentum. (Figure 2B) The tumor was approximately 30 – 40% necrotic. The patient was hospitalized for 36 days with postoperative complications including aspiration pneumonia and tracheitis requiring tracheostomy and episodes of encephalopathy attributed to anesthesia hypersensitivity. After discussion at our institution's tumor board meeting, a consensus was formed that further treatment should be an alternate to traditional chemotherapy, given the patient's previous hypersensitivity reaction and positive hormone receptors. A regimen of tamoxifen and medroxyprogesterone was started.

Four months postoperatively, hyperfractionated radiation treatment totaling 3000 cGy was completed in a 2-week interval and the tissue expanders were removed. Follow up CT scan of the abdomen at this time revealed the hepatic lesion no longer seen, improved right hydronephrosis with no soft tissue mass or adenopathy.

A chest CT scan, taken 19 months postoperatively, showed no tumor. There was slight right hydronephrosis with no evidence of ascites or masses in the abdomen and pelvis. Incontinence remains an issue for the patient who requires a foley catheter with leg bag and fiber supplements for fecal urgency. The patient has recently received erythropoietin and cyanocobalamin for anemia. The patient remains functional at two years post pelvic perfusion and one and a half years after resection of recurrent

drug levels and overcome the expression of drug resistance mechanisms, such as the MDR1 gene found to be strongly expressed in chemotherapy resistant cancers.⁸

The high leak rate of drug into the systemic circulation remains a limitation to treatment because of potential marrow suppression. Drug leakage is extremely variable and may be reduced by wash-out of the pelvic circuit with or without blood transfusion, by maintaining systemic hypertension (higher systemic pressure than pelvic pressure) or chemofiltration during extracorporeal bypass to reduce toxic drug levels in the systemic circuit.⁹ Unfortunately, the results of all of these techniques for systemic protection are not reproducible. The use of stem cell support provides a method of bone marrow rescue to obviate the myelotoxicity of the high dose chemotherapy. Stem cells may be derived from the blood stream as well as from the bone marrow. A **bone marrow transplant (BMT)** may be autologous (from the same patient) or allogeneic (from a different subject). The simultaneous administration of hematopoietic stimulating factors such as G-CSF may accelerate marrow re-growth. This technique has been successfully used as treatment of several hematologic malignancies; however, its role in the management of solid tumors is still under investigation.¹⁰

There are few reports in the literature concerning high dose chemotherapy with bone marrow rescue for endometrial cancer. This treatment has been controversial when applied to stage 4 breast cancer, which tends to invade the marrow space.¹¹ The most important issues that face the success of high dose chemotherapy and rescue BMT include re-infusion of malignant cells from the auto-transplant, marrow aplasia, chemoresistant cancer cells and preexisting heavy tumor burdens with distant metastases.^{11,12} There are reports of long term survival with high dose adjuvant chemotherapy and autologous hematological rescue for ovarian and breast carcinoma.^{12,13,14} One study showed 72% three year survival for patients with breast cancer and greater than 10 positive nodes after chemotherapy treatment, rescue BMT and surgery. It also showed an 80% complete remission rate in patients with inflammatory breast cancer.¹⁴ To our knowledge, our patient is the first reported case in whom high-dose chemotherapy was delivered with isolated pelvic perfusion and bone marrow rescue for advanced gynecologic malignancy. Of note, we have also utilized bone marrow retrieval in another patient with locally advanced penile melanoma who had high dose LPAM delivered via isolated pelvic perfusion and had a clinical response followed by surgical resection. Although complete response in melanoma patients treated with high-dose chemotherapy and marrow rescue is limited, responding patients may benefit with long-term survival.¹⁵

The combination of bone marrow support following isolated pelvic perfusion has been shown to be of potential future value. These treatment modalities for gynecologic and other solid tumors should be evaluated in randomized prospective studies to gain a more precise understanding of the long-term survival for these patients.

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Advances in Pharmacology

New Monoclonal Antibodies For Hematologic Malignancies (and Breast Cancer)

Mark A. Curtis, RPh

Over the last few years advances in monoclonal antibody technology have brought a new class of anti-cancer agents into clinical practice. Because antibodies are biochemically highly specific for antigens that are relatively small portions (epitopes) of considerably larger molecules, monoclonal antibodies are the forerunner of the class of "targeted" drugs. The monoclonal antibodies that have made it into clinical practice bind to epitopes that are present (expressed) or overexpressed on tumor cells. Currently available monoclonal antibodies are not directed to tumor specific epitopes (tumor specific antigens), but to normal molecules that are present on tumor cells (tumor associated antigens). They have made it into clinical practice because of demonstrable anti-tumor activity and diminished side effect profiles when compared to traditional chemotherapeutic agents. Four examples of these compounds are rituximab (Rituxan®), trastuzumab (Herceptin®), denileukin diftitox (Ontak®) and alemtuzumab (Campath®). (Table 1)

Approved by the US Food and Drug Administration (FDA) in November 1997, rituximab, (Rituxan®), was the first monoclonal antibody approved for treating cancer in the United States. Rituximab is in a class of murine/human chimeric monoclonal antibodies with specificity for the CD20 surface marker on B cells. During the early pre-B-cell development human B-lymphocyte-restricted differentiation antigen is expressed. This expression is seen on

at least 90% of B-cells in non-Hodgkin's lymphomas. By binding to the CD20 surface marker on these B-cells, rituximab mediates antibody-dependent cellular cytotoxicity and complement-dependent tumor cell lysis.

Rituximab is useful in the treatment of low-grade/follicular CD20 positive B-cell non-Hodgkin's lymphoma, in patients with relapsing disease or who are refractory to conventional chemotherapy. Rituximab can be used as an-add on to conventional therapy or even as a first-line therapy for B-cell lymphomas or to treat other malignancies with CD20-antigen expressions, as seen in some chronic lymphocytic leukemias.

Trastuzumab (Herceptin®), approved by the FDA in September 1998, is a humanized anti-p185-HER2/neu monoclonal antibody used for the treatment of HER2/neu positive metastatic breast cancer. Trastuzumab selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor two protein (HER2/neu). Trastuzumab is immunoglobulin-1 (IgG₁) based and inhibits the growth of human breast cancers that exhibit over expression of p185-HER2/neu. It induces antibody-dependent cell-mediated cytotoxicity very selectively on these cells. This activity makes trastuzumab useful only in breast cancers with HER2/neu protein over expression.¹

Denileukin diftitox (Ontak®) was approved by the FDA February 5, 1999, for the treatment of persistent or recurrent cutaneous T-cell lymphoma whose malignant cells

express the CD25 component of the IL-2 receptor. Denileukin diftitox is an interleukin-2 receptor specific ligand fusion protein incorporating diphtheria toxin fragments A and B fused to interleukin-2. In interleukin-2 receptor-expressing malignancies (i.e. certain leukemias and lymphomas) denileukin diftitox binds to the interleukin-2 re-

TABLE 1: COMPARING FDA APPROVED MONOCLONAL ANTIBODIES

NAME	DATE FDA APPROVED	TARGET	DISEASE TREATMENT	AWP CONCENTRATION (AWP COST/WEEK)	ADVERSE REACTIONS
Rituximab (Rituxan®)	11/1997	CD20 surface marker on B cells	Relapsed or refractory low grade or follicular (27%) positive B-cell Non-Hodgkin's lymphoma	\$2500.00 per 500 mg vial 12 vials for patients over 1.33 m ² \$3,000.00/week	The most serious adverse reactions include infusion reactions, myelosuppression, chills, rashes, reactions, hypersensitivity, cardiac arrhythmia, angioneurotic edema, and fever
Trastuzumab (Herceptin®)	9/1998	Anti-p185-HER2 protein	Metastatic breast cancer with overexpression of the HER2 protein and have received one or more chemotherapy for their metastatic disease	\$2544.78 per 440 mg vial 170 kg uses 280 mg biweekly & 140 weekly or \$2844.78/week	Fatigue, bone pain, arthralgia, myalgia, dyspnea, wheezing, pleuritis, edema, pulmonary edema, fever, chills, nausea, vomiting, hypotension, headache, development of ventricular dysfunction and CHF
Denileukin Diftitox (Ontak®)	2/5/1999	CD25 component of IL-2 receptor	Recurrent refractory cutaneous T-cell lymphoma expressing the CD25 component of the interleukin-2 receptor	\$637.00 per 150 mg vial 170 kg uses 9 vials at 9 to 18 mg/kg x 5 days or \$15,810.00/week \$11,850.00 per course	Fever, chills, and chills, flu-like symptoms, anemia, rashes, swelling, hypotension, hypalbuminemia, hypokalemia, edema, skin rash, and transaminase elevation or elevation
Alemtuzumab (Campath®)	5/1999	24-28 kD cell surface glycoprotein, CD52	B cell chronic lymphocytic leukemia that have been treated with alkylating agents and have failed fludarabine therapy	\$564.50 per 10 mg ampule 19 vials per week at maximum dose or \$5,825.50 per week	Infusion related events including hypotension, bradycardia, vomiting, fever, chills, rigors and rash, myelosuppression, opportunistic infections, and severe and prolonged hematologic toxicity

ceptor and is transported into the cell via a receptor-mediated endocytosis. In the cytosol the enzymatically active fragment A portion of the diphtheria toxin inhibits protein synthesis which results in the death of the cell.

Alemtuzumab (Campath®) is a recombinant DNA-derived humanized monoclonal antibody, approved on May 7, 2001, directed against the 21-28 kD cell surface glycoprotein, CD52. CD52 is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and tissues of the male reproductive system. The Campath-1H antibody is an IgG₁-kappa molecule with a human variable framework, constant regions, and complementarity-determining regions from a murine (rat) monoclonal antibody (Campath-1G). Alemtuzumab is used in the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with and failed alkylating agents and fludarabine therapy. By specifically binding to the CD52 antigen on malignant lymphocyte, alemtuzumab induces cell lysis.

Therapies developed using monoclonal antibody technologies offer cell specific treatment for certain types of cancer and are often well tolerated. These four agents, while costly, are just the beginning of highly directed chemotherapy.

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Pneumococcal Immunization of Hospitalized Patients

Dede Ordin, MD, MPH

There is little controversy in the medical community over the importance of administering pneumococcal polysaccharide (PPV) and flu vaccine to high-risk populations. These immunizations are usually provided in outpatient settings, but immunization of hospitalized patients who have not been vaccinated previously can enhance immunization rates in a group at particularly high risk. Despite the demonstrated effectiveness of inpatient immunization programs (as described below), some Rhode Island physicians have expressed concern regarding immunization of vaccine-eligible patients hospitalized for surgery or an acute illness. Recently, discussion of this issue has become more prominent in many hospitals, since inpatient PPV immunization rates (at present calculated only for patients hospitalized for pneumonia) are included in Rhode Island's publicly reported measures of hospital quality and will be reported nationally by the Centers for Medicare & Medicaid Services (CMS) later this year. In this article, I address some of the issues raised by Rhode Island physicians regarding administration of PPV to hospitalized patients.

Why do we need to provide PPV to patients in the inpatient setting? Shouldn't they be getting the vaccine in their physicians' offices?

Ideally, all persons eligible for the vaccine should be immunized in the outpatient setting, but this does not always happen. In a recent national study, only one-third of Medicare patients hospitalized for pneumonia, myocardial infarction, heart failure, or stroke in 1998-1999 had received PPV prior to admission. The situation is likely to be somewhat better in Rhode Island, where approximately 67% of those age 65 and older have received PPV. However, if 67% are immunized, this means that nearly one-third of this high-risk group has not been immunized in their physicians' offices. In fact, 11% of Rhode Island adults, including 6% of people 65 years and older, report no regular source of primary care, and this proportion is even larger among Rhode Island's minority populations.³ For these people a hospitalization (or emergency room visit) may afford the most expedient opportunity to provide the vaccine.

Does the Centers for Disease Control and Prevention (CDC) currently recommend inpatient administration of PPV to hospitalized high-risk patients?

Yes. CDC's Advisory Committee on Immunization Practices encourages inpatient administration of PPV, noting that this strategy is effective and capable of reaching those patients

most likely to develop pneumococcal disease.⁴ The target population (i.e., those at high risk for increased morbidity and mortality related to pneumococcal disease), is the same for inpatient and outpatient immunization and includes persons age 65 or greater, immunocompetent persons age two or greater at increased risk because of chronic illnesses, functional or anatomic asplenia, or living in environments in which the risk for disease is high (e.g., daycare centers), and immunocompromised persons age 2 or greater. CDC recommends onetime revaccination after five or more years for two groups: persons aged 65 or older vaccinated before the age of 65; and previously vaccinated persons aged 64 years or younger who are immunocompromised secondary to underlying medical conditions or medications. CDC notes that, for other high-risk populations, the need for subsequent doses of pneumococcal vaccine is unclear and will be assessed when additional data become available.

What are the potential adverse effects of inpatient administration of PPV?

Adverse reactions associated with inpatient PPV administration are similar to those in the outpatient setting and consist primarily of local reactions (i.e., pain, erythema, swelling) at the injection site. In a 1994 meta-analysis of nine randomized controlled outpatient trials of PPV efficacy, one-third of the 7531 patients receiving the vaccine had local reactions. There were no reports of severe febrile or anaphylactic reactions nor any reported neurologic disorders (e.g., Guillain-Barre syndrome).⁵

Which high-risk patients should NOT receive the vaccine in the hospital?

High-risk patients who have received the vaccine within the previous five years do not need to receive the vaccine. The manufacturer recommends that, if possible, patients undergoing splenectomy or receiving cancer chemotherapy or other immunosuppressive therapy should receive the vaccine at least two weeks before initiation of therapy. The safety of PPV during the first trimester of pregnancy has not been evaluated. At some hospitals, physicians have expressed concern over the theoretical possibility of an anaphylactic reaction to the vaccine and thus are reluctant to immunize patients who are hemodynamically unstable or in respiratory distress; some physicians have also questioned the efficacy of the vaccine in patients with febrile respiratory illness or other active infection. These precautions are noted in the *Physicians' Desk Reference*, although I am aware of no published documentation that vaccine-associ-

ated adverse events have occurred in these situations. In any event, these concerns may be circumvented by immunizing patients at the time of discharge.

What should be done if a patient does not know whether he/she has previously received PPV?

According to current CDC recommendations, providers should not withhold vaccination in the absence of an immunization record or complete medical record. The patient's (or family's) verbal history should be used to determine prior vaccination status. When indicated, vaccine should be administered to patients who are uncertain about their vaccination history.⁴ Revaccination fewer than five years after initial PPV immunization results in a greater incidence of local reactions but has not been associated with any increased risk of systemic reactions.

How can busy physicians be expected to remember to order the vaccine for their hospitalized patients?

Immunization is seldom at the forefront of physician concerns during a patient's hospitalization. Successful inpatient immunization programs utilize either standing orders or reminder systems, thus obviating the need to rely solely on physicians' spontaneously remembering to order immunization for eligible patients. Standing orders for inpatient immunization are permissible under both Rhode Island law and Medicare regulations. In most standing order programs, a nurse screens patients to determine whether they meet the vaccine eligibility criteria. If the patient is determined to be eligible, the nurse activates the standing order and administers the vaccine, usually at discharge. Reminder systems involve screening for vaccine eligibility by nurses, pharmacists, or infection control practitioners, and placement of a highly visible reminder on the chart (or a message incorporated into a computerized order entry system) to remind physicians to order the immunization. These approaches have been reported to increase administration of PPV to vaccine-eligible patients by 29 to 78 percentage points.^{6,7,8,9}

Is assistance available to Rhode Island hospitals working to increase their inpatient immunization rates?

Quality Partners of Rhode Island can provide literature, slide presentations, examples of standing orders, and general quality improvement consultation to help hospitals and physician offices increase patients' PPV and influenza immunization rates.

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The author assumes full responsibility for the accuracy and completeness of the ideas presented. This article is a direct result of the Health Care Quality Improvement Program initiated by the Centers for Medicare & Medicaid Services, which has encouraged identification of quality improvement projects derived from analysis of patterns of care, and therefore required no special funding on the part of this Contractor. Ideas and contributions to the author concerning experience in engaging with issues presented are welcomed.

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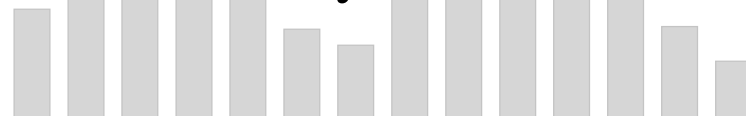
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Health by Numbers



Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Edited by Jay S. Buechner, PhD

Violent Deaths in Rhode Island, 1999-2002

Jay S. Buechner, PhD, Elizabeth A. Laposata, MD, Wendy Verhoek-Ofstedahl, PhD, Edward F. Donnelly, RN, MPH

In 2000, there were nearly 51,000 deaths nationally caused by non-accidental violence, including homicides, suicides, and other violence.¹ Other major categories of injury deaths have federally-supported data systems drawing on multiple sources to support epidemiologic studies and program evaluations, despite comprising fewer deaths per year than violence. For motor vehicle deaths, the **National Highway Traffic Safety Administration (NHTSA)** has sponsored the **Fatality Analysis and Reporting System (FARS)** for several decades. For occupational injury deaths, the Bureau of Labor Statistics developed the **Census of Fatal Occupational Injuries (CFOI)** early in the last decade.

The Institute of Medicine recommended that a similar system be developed for violent deaths in its 1999 report, *Reducing the Burden of Injuries*.² In response, the Injury Control Research Center at the Harvard School of Public Health, with support from the **Centers for Disease Control and Prevention (CDC)**, performed a pilot study, the **National Violent Injury Surveillance System (NVISS)**, which included both fatal and non-fatal injuries. Subsequently, Congress mandated the development of the **National Violent Death Reporting System (NVDRS)** in the FY2002 federal budget. In the first year of the NVDRS, the CDC enrolled six states; in FY2003, Congress appropriated funding to add eight more states. As designed by the CDC, the NVDRS assembles and links information on each violent death from four sources: Death certificates, Medical Examiner investigations, police crime reports, and crime laboratory findings. The Rhode Island Department of Health has applied to join the NVDRS and has analyzed death certificate data and Medical Examiner data for 1999-2002 in support of its application.

Methods

Violent deaths occurring in Rhode Island in 1999-2002 were identified in the Vitals Records death files using the **underlying cause of death (UCOD)** codes specified by the NVDRS. (Table 1) Cases were aggregated by patient demographics (age, sex, race, and place of residence) and by information from the UCOD on intent to injure (assault, self-inflicted, unintentional, undetermined) and mechanism of injury (firearms, suffocation, poisoning, etc.).³ [Note: The large

majority of deaths of undetermined intent are deaths due to overdoses of drugs, including prescription, over-the-counter, and illegal drugs, where possible suicidal intent and accident could not be distinguished. Such deaths are included in the broad definition of violence used in the NVDRS.]

Results

There were 776 deaths in Rhode Island during 1999-2002 that meet the NVDRS definitions for violent deaths, an average of 194 deaths per year. Of these, the largest proportion were suicides (82.5 per year), followed by deaths from drug overdoses or other undetermined intent (66 per year),

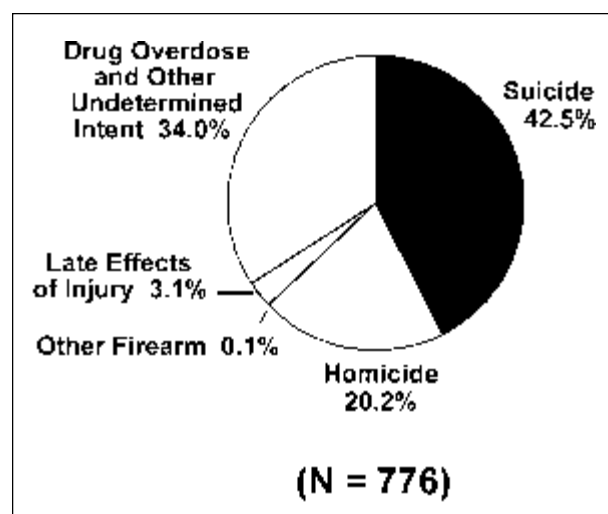


Figure 1. Proportion of violent deaths by NVDRS category, Rhode Island occurrences, 1999-2002.

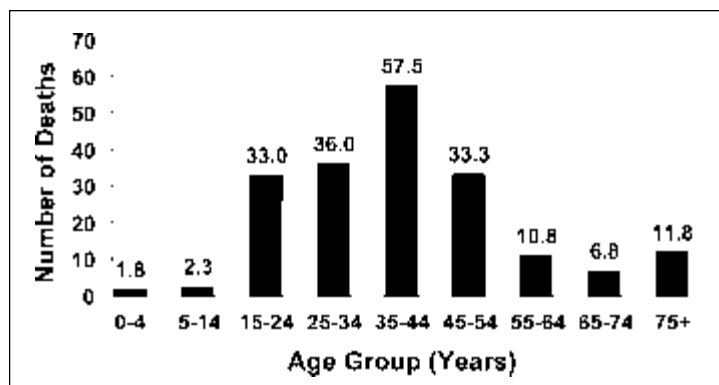


Figure 2. Annual average number of violent deaths, by age group, Rhode Island occurrences, 1999-2002.

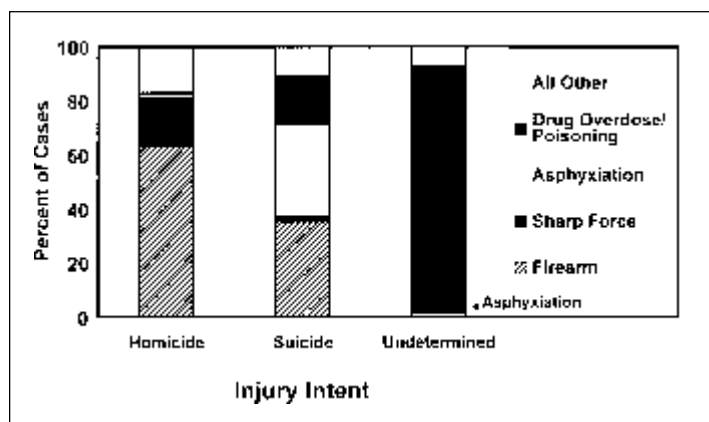


Figure 3. Proportion of violent deaths by mechanism of injury and intent, Rhode Island occurrences, 1999-2002.

Table 1.
Definition of Cause of Death Groups Used by the National Violent Death Reporting System

Cause of Death	ICD-10* Codes
Suicide	X60-X64, Y87.0
Homicide	X85-Y09, Y87.1
Undetermined intent	Y10-Y34, Y87.2
Legal intervention	Y35, Y89.0
Other firearm	W32-W34
Late effects of injury	Y86, Y89.9

*International Classification of Diseases, 10th Revision.

homicides (39.3 per year), late effects of injuries (6.0 per year), and other firearms injuries (0.3 per year). (Figure 1)

Violent deaths in the state were clustered among residents ranging in age from adolescence to middle age. (Figure 2) Median age at death was 38 years; median ages for suicides (41 years) and deaths from drug overdoses or other undetermined intent (40 years) were higher than for homicides (27 years). By gender, 74.2% were male. By race and ethnicity, the proportion of violent deaths among African-Americans (10.6%) was higher than the proportion of African-Americans in the 2000 Census for Rhode Island (4.5%).

The mechanism of injury varied greatly according to the characterization of intent. Among homicides, the majority of deaths (63.7%) were caused by firearms injuries; among suicides, the proportion caused by firearms was lower (35.5%), and there were no deaths of undetermined intent from firearms. (Figure 3) Deaths caused by sharp force such as knives were most common among homicides (17.2%), much less common among suicides (1.8%), and not appearing at all among deaths of undetermined intent. Conversely, there were no homicides by drug overdoses or poisoning, but this category comprised the third most common mechanism of suicide (17.6%) and nearly all (91.7%) deaths of

undetermined intent. Death by asphyxiation (hanging, suffocation) was far more common among suicides (34.2%) than among homicides (1.8%) or deaths of undetermined intent (1.1%).

Discussion

Death rates for injuries, including violent injuries, are generally lower in Rhode Island than nationally,⁴ but these deaths occur among residents in their most productive years and hence represent a substantial burden of premature mortality. It is likely that many of these deaths are preventable through a variety of proven public health interventions that address violent and suicidal behaviors and complement law enforcement, mental health, and substance abuse prevention activities.

If the Rhode Island application to participate in the NVDRS is successful, the substantial additional information assembled on the violent deaths occurring here will meet a number of goals. It will help reveal the underlying patterns of violence and suicide, support the development of violence and suicide prevention strategies and programs, and allow the scientific evaluation of those programs' success. Participation in the NVDRS will help establish partnerships between public health and other organizations involved in violence prevention in the state and municipalities, notably law enforcement agencies. And it will enhance federal-state collaborations against violence through the sharing of surveillance data and evaluation results.

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– A Physician's Lexicon –



Sex, Sex, Sex

While admittedly they view sex from different vantage points, both the biologist and the adolescent male will insist that sex [or gender] is a vitally important subject. Even the etymologist, whose passion is generally restricted to old dictionaries, is bedazzled by the linguistic fertility of the words cognate with gender or sex.

Gender, a sometime synonym of sex, is here defined as a set of biological classes such as masculine and feminine. The word is derived from the Latin *genus*, variously meaning class, category, gender or race and is descended from an earlier Indo-European root *gen-*, with a somewhat broader meaning of family, union, male or even father.

There is an abundance of English words stemming from this Indo-European root, including genus [a specified class or subdivision], engender [to produce or plant], gene, genetic, genealogy, general [pertaining to all persons or things, a non-inclusive designation], general [as a mili-

tary rank], generate, generation, generic [something applicable to all members of a class; but currently, a word signifying those items, such as pharmaceuticals, in the class not protected by a trademark], generous [from the Latin, *generosus*, initially meaning of noble birth, later meaning magnanimous], genesis, genius, and of course genital. Then too there is the French word, *gendarme*; it had originally been spelled, *gen d'armes*, meaning men of arms.

All of the words that are derived from *gen-* convey the sense of class and sometimes maleness, but also the sense of fertility or generativeness [breaking a basic rule: never use the word to be defined in its definition]. And yet through extended usage, some of these words have evolved into meanings that contradict the original intent of the root. A military general, for example, is clearly not a member of an all-inclusive class [as in the phrase, general public].

The word sex, to define the female or male elements of a species, is derived from the Latin *secare*, meaning to divide or cut, as in words such as sect, venesection, bisect and scissors.

And finally, the word gamete, defining those cellular elements, such as sperm and ovum, capable of conjugation. It descends ultimately from a Greek word meaning marriage, as in the English word monogamy. Bigamy describes two concurrent marriages, while digamy defines a second marriage, but only after the dissolution of the first.

To those finding this column wanting, please remember the words of Ortega y Gasset: "Nine-tenths of that which is attributed to sexuality is the work of our magnificent ability to imagine."

– Stanley M. Aronson, MD, MPH



Vital Statistics

Rhode Island Department of Health

Patricia A. Nolan, MD, MPH, Director of Health

Edited by Roberta A. Chevoya

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data
from the
Division of Vital Records

Underlying Cause of Death	Reporting Period			
	August 2002	12 Months Ending with August 2002		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	206	2,933	279.8	3,906.5**
Malignant Neoplasms	178	2,318	221.1	6,801.5
Cerebrovascular Diseases	36	512	48.8	715.0**
Injuries (Accident/Suicide/Homicide)	30	399	38.1	7,560.5***
COPD	30	493	47.0	470.0**

Vital Events	Reporting Period		
	February 2003	12 Months Ending with February 2003	
	Number	Number	Rates
Live Births	818	12,955	12.4
Deaths	875	10,346	9.9
Infant Deaths	(6)	(95)	7.3
Neonatal deaths	(5)	(66)	5.1
Marriages	405	8,389	8.0*
Divorces	263	3,314	3.2
Induced Terminations	446	5,590	431.5#
Spontaneous Fetal Deaths	68	1,010	78.0
Under 20 weeks gestation	(67)	(940)	72.6
20+ weeks gestation	(1)	(70)	5.4

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,048,319

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population

Rates per 1,000 live births

** Excludes one death of unknown age.

*** Excludes two deaths of unknown age.

Quality *is* Worth More W



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NINETY YEARS AGO

✿ [AUGUST, 1913] ✿

An Editorial on The Board of Optometry described the stringent examination questions for opticians: "Without a Webster's Unabridged, we doubt if a member of the Board could correctly answer them all and they are as pertinent to the science of refraction as the Binominal Theorem is to the high cost of living." Not one of 7 candidates passed. Questions included: "What is asthenopia? How many kinds? Name each and give symptoms and how found. What is toxic amblyopia? Photonusus? Trachema? Nystagmus? How many kinds? Explain the difference in corectasis, corectopia, coredialysis, corelysis." The Editorial took solace in the exclusionary bent of the exam: "It may be a shrewd end method of restricting the number of competing opticians, and if so the plan has our hearty admiration."

James S. Cotton, DDS, in "A Plea of Relief from Suffering Due to Neglect of Children's Teeth," asked readers to adopt the axiom: "A child's health can be only as good as his teeth." Over 90% of public school children in America had diseased teeth; in Providence, 80% of second and third-graders had diseased teeth. As dental inspector for Providence schools, Dr. Cotton notified 2148 parents during 1911 of problems with their children's teeth; 23% of parents responded, arranging for 1099 dental operations; but Dr. Cotton noted that many parents could not afford a dentist.

At the Medical Society annual meeting, trustees of the Chase Wiggin Fund offered a prize of \$50 for the best popular essay on "Tobacco and its Evil Effect in All its Forms on Those Who Habitually Use It."

FIFTY YEARS AGO

✿ [AUGUST, 1953] ✿

George M. Wheatley, MD, MPH, the third Vice President, Metropolitan Life Insurance Company, and Chairman, Accident Prevention Committee, American Academy of Pediatrics gave "The Practicing Physician and Accident Prevention," the 12th Annual Charles V. Chapin Oration. Citing Charles Chapin's admonition: "Accidents are more preventable than disease," Dr. Wheatley cited the "menace of the machine," including cars, workplace machines, farm equipment and home workshop tools. In 27 states, medical societies distributed "safety vaccine" pam-

phlets to physicians. The pamphlets gave physicians a checklist to use with parents during home visits.

Eske Winsberg, MD, FACS, in "Intussusception, Retrograde (Ileo-Ileal) with Aseptic Strangulation Necrosis," described this rare occurrence in a 40 year-old woman admitted to Miriam Hospital. For four days prior to admission she had had abdominal pains and vomiting. An operation revealed the intussusception. The patient, discharged after 14 days, recovered.

An Editorial, "Malpractice is Your Problem," stressed the need for physicians to have insurance.

A second Editorial, "Midsummer Madness," noted that, where 32,000 Americans were killed in the Korean War, 38,000 were killed in car accidents last year. The American Medical Association advised physicians to counsel patients "who they believe should not operate a motor vehicle," especially "those with mental instability."

TWENTY FIVE YEARS AGO

✿ [AUGUST, 1978] ✿

In a Message from the Dean, Stanley M. Aronson, MD, I described "The Early Identification Program for Providence College and University of Rhode Island students." Of 480 students in the first 8 medical school classes, 143 were Rhode Islanders. Of 243 graduates, 53 (22%) were Rhode Islanders. In sum, 13 Rhode Island students have entered Brown via the EIP.

James E. Hickey, Chief, Division of Occupational Health and Radiation Control, RI Department of Health, contributed "Patient exposure during diagnostic x-ray procedures in RI: A Report of the RI NEXT Program." The federal government had spearheaded a study of x-ray trends in 46 states. As part of that study, the RI Radiation Control Agency surveyed 100 x-ray facilities. The journal reported those findings.

Harilaos T. Sakellarides, MD, in "The Extensor Tendon Injuries and the Treatment," noted that "injuries have a good prognosis with appropriate management."

Frederick C. Pearson, PhD, Associate Professor of Biology, Providence College, described "The Liniculus Amebocyte Lysate Test: Present and Future Application." The test provides "a means of detecting and assaying gram-negative endotoxin in a variety of settings."