Use of Monoclonal Antibodies in Oncology

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Monoclonal antibodies (MCA) represent a significant addition to therapeutic options for a number of oncologic disorders. MCA are highly specific. They bind to and affect disease specific targets resulting in sparing of normal cells with less side effects than traditional chemotherapy. This review focuses on MCA approved for clinical use.

MCA are produced by a single clone of B cells and are mono specific. These antibodies can block essential cellular receptors, directly induce apoptosis, bind to target cells, and recruit antibody-dependant cellular or complement-dependent cytotoxicity mechanisms. They can also deliver cytotoxic chemicals such as radioisotopes and toxins. The pharmacologic characteristics are summarized. [Table 1]

The **Food and Drug Administration (FDA)** has approved several MCA for oncologic indications.

Rituximab

Rituximab was the first approved MCA. This chimeric IgG molecule binds with high specificity to the CD20 molecule on lymphoid cells of B lineage. Rituximab is active against CD20 positive **Non Hodgkins Lymphoma (NHL)**.

Low Grade Non Hodgkins Lymphomas

In a pivotal phase II trial, heavily pretreated patients with relapsed low grade NHL were given single agent rituximab intravenously weekly for four weeks. Forty eight percent of patients responded with a median response of 12 months.[1] After retreatment the response rate was around 40%.[2] Rituximab was found to be effective and safe when combined with standard first line chemotherapy. In the phase III trial involving CD20 positive follicular NHL patients the response rate was 81% in the combination group (**Cyclophosphamide, Vincristine and Prednisone (CVP)**

Table 1.

Monoclonal Antibody	Target	Mechanism	Indication	US FDA Approval Date	Adverse Reaction
Rituximab (Rituxan)	CD 20	ADCC, CDC, Directly induces apoptosis	NHL Maintenance in NHL	11/26/1997 1/28/201	Allergic Reactions Tumor Lysis Syndrome
Trastuzumab (Herceptin)	HER 2	Inhibition of HER2-mediated tumor cell proliferation and migration	Breast Cancer	9/25/1998	Cardiac complications Allergic reactions
Cetuximab (Erbitux)	EGFR	Inhibits EFGR mediated tumors cell invasion, proliferation metastatis, Enhances Activity of some chemotherapuetic and radiotherapy	Colon Head and neck cancer	2/12/2004 3/1/2006	Allergic reactions and skin rash
Penitumumab (Vectibix)	EGFR	Inhibits EFGR mediated tumors cell invasion, proliferation metastatis,	Colon	9/27/2006	Dermatologic toxicity
Bevacizumab (Avastin)	VEGF	Inhibiton of VEGF induced angiogenesis	Metastatic Non squamous lung Colon Met Renal cell ca Recurrent gliomas Met Breast	10/11/2006 2/26/2004 7/31/2009 5/5/2009 12/16/2010	Proteinuria Hypertension Thrombosis Reduced wound healing Pulmonary Hemorrhage in squamous histology
Alemtuzumab (Campath)	CD 52	ADCC, CDC	CLL	5/7/2001	Pancytopenia, Lymphopenia

with Rituximab) vs. 57 % in patients given CVP alone [P = < 0.001]. Time to treatment failure was longer in the combination group 27 vs. seven months [P = < 0.001]. Benefit was not associated with any significant increase in toxicity.[3]

In January 2011 the US FDA approved Rituximab for maintenance therapy for previously untreated CD20 + B cell NHL that achieved a response. This was based on the **PRIMA study** (**Primary Rituximab and Maintenance Phase III intergroup trial**). After achieving a response to systemic chemotherapy, 1018 patients were randomized in a 1:1 manner to receive either rituximab 375 mg/m2, intravenously every eight weeks with a maximum of 12 doses vs. observation. **Progression free survival** (**PFS**) was the primary endpoint and treatment. Rituximab increased PFS by 46 % [P = < 0.001]. A higher percent of patients had a complete response at 2-4 months with Rituximab maintenance [67 vs. 48 %].[4]

High Grade Non-Hodgkins Lymphoma

In a randomized phase III study of **Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone** (**CHOP**) chemotherapy with or without rituximab in treatment naive patients, the rituximab arm showed a higher PFS, (53 vs. 35 % P = 0.0008) without increased toxicity.[5,6] A phase III study, the MabThera International Trial (or MInT trial), enrolled patients with high grade lymphoma, aged 18-60 years and compared CHOP plus rituximab with chemotherapy alone as first line treatment . The study was closed early when interim analysis showed a significantly longer time to treatment failure in the combination group. After a follow up of 34 months patients assigned to R-CHOP had significantly higher PFS, (79% vs. 59%) and overall survival OS, [93% vs. 84%].[7]

Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia

Rituximab is also active in **Chronic Lymphocytic Leukemia** (**CLL**).[8] In a phase II study by the Cancer and Leukemia Group B, fludarabine plus Rituximab based therapy in previously untreated patients gave a higher response rate and complete remission than chemotherapy alone.[9]

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that targets HER2 also known as C-erb-B2, a member of the EGFR family. HER2 is over expressed in about 25-30% of breast cancer. Over expression in early stage breast cancer is associated with poor prognostic factor such as high tumor grade,[10] axillary lymph node involvement,[11] increase mitotic rate,[12] and lack of estrogen and progesterone receptor expression.[13] It is also an independent adverse prognostic factor.[14]

In a phase III trial patients with **metastatic breast cancer** (**MBC**) with HER2 over expression, untreated patients were randomized to receive standard chemotherapy with and without Trastuzumab. Those who received Trastuzumab plus chemotherapy had a longer time to disease progression, 7.4 months vs. 4.6 months [P = < 0.001], a highly objective response rate, 50% vs. 32% [P = < 0.001], a longer median duration of response, 9.1 vs. 6.1 months, [P = < 0.0001], longer median survival, 25.1 months vs. 20.3 months [P = 0.046], and a 20 % lower risk of death than patients who had received chemotherapy alone.[15]

Addition of trastuzumab to adjuvant chemotherapy significantly reduces the likelihood of disease relapse and death among women with HER2 positive early stage breast cancer. Two North American cooperative group trials were designed to evaluate the efficacy of adjuvant trastuzumab. In the **National Surgical Adjuvant Breast and Bowel Project trial** (**NSABP B-31**), 1736 patients with Her2 positive breast cancer received 4 cycles of doxorubicin and cyclophosphamide [AC] followed by four cycles of paclitaxel 175mg/m2 every three weeks. They were randomly assigned to no further therapy or weekly trastuzumab beginning with the first course of paclitaxel. The **North Central Cancer Treatment Group** (**NCCTG trial N9831**) tested the value of adding trastuzumab to sequential AC and paclitaxel in concurrent vs. sequential trastuzumab and paclitaxel. In this trial, 1615 women with HER2 positive lymph node or high risk node negative breast cancer (greater than 1cm ER negative or greater than 2cm ER positive) received AC in one of the three different treatment strategies. Weekly paclitaxel for 12 weeks alone, weekly paclitaxel followed by trastuzumab for 52 weeks, or weekly paclitaxel with concurrent trastuzumab followed by trastuzumab alone for 40 weeks.[16,17] Combined analysis demonstrated that adjuvant trastuzumab paired with paclitaxel chemotherapy resulted in a greater than 50 % reduction in recurrence risk, with a four year disease free survival of 86% vs. 73% and a 37% reduction in risk of death. The four year overall survival was 93% vs. 89%. This led to FDA approval and established adjuvant traztuzumab as the standard of care.[18] Similar results were found in early analysis of a large multinational trial, the **Herceptin Adjuvant study** (**HERA trial**).[19]

Trastuzumab is associated with the risk of cardiotoxicity manifested by an asymptomatic decline in the left ventricle ejection fraction and less commonly development of New York Heart Association Class III or IV.[20] The cardiac toxicity may be reversible in many patients and responds to standard treatments for heart failure. Anthracycline use and age greater than 60 years are the strongest risk factors for development of trastuzumab-related cardiac toxicity.

Cetuximab

Epidermal Growth factor Receptor (**EGFR**) also known as HER-1 is a tyrosine kinase receptor and a member of the EFGR family. Over-expression is seen in various epithelial tumors such as lung, breast, head and neck and colon. Over expression is associated with a poor prognosis.[21-23]

Metastatic Colorectal Cancer (CRC)

Cetuximab is a chimeric monoclonal antibody that binds to EGFR, blocking its binding to its receptor thus preventing receptor activation and downstream signaling. Two monoclonal antibodies that target EFGR are active for treatment of metastatic colorectal cancer, cetuximab and panitumamab. KRAS, the protein product of the Ras oncogene, serves as a mediator between extracellular ligand binding and intracellular transduction signals from EGFR to the nucleus. Activating KRAS mutations are detected in approximately 40% of metastatic colorectal cancer, with good concordance between the primary and distant metastasis.[24] KRAS mutations are associated with poor prognosis and overall resistance to

EGFR therapy. Panitumumab and Cetuximab are approved only for patients with wild type KRAS tumors. KRAS mutation analysis is commercially available.

Cetuximab monotherapy was compared to best supportive care in a randomized trial of 572 heavily pretreated patients with Metastatic CRC.[25] Median OS was significantly better with cetuximab (6.1 vs. 4.6 months), and quality of life measures were also improved in the treatment arm. In a subsequent analysis, the benefit of Cetuximab was restricted to patient who lacked KRAS mutation (wild type KRAS). Cetuximab has also been used with chemotherapy with encouraging results.[26] First line Cetuximab was evaluated in patients with previously untreated metastatic CRC, 1198 were randomized to **5-FU, leucovorin, and irinotecan (FOLFIRI)** with or without Cetuximab.[27] Median PFS was modestly better in patients with combined therapy, 8.9 vs. eight months, as was the overall response rate (47% vs. 39%). However there was no significant difference in OS. In a preliminary report in patients with wild type KRAS, response rates were significantly higher in those who received cetuximab in conjunction with chemotherapy.[28] Cetuximab is indicated only for patients with wild type KRAS tumors.

Panitumumab is fully human monoclonal antibodies specific for the extra cellular domain of EGFR. Panitumumab is approved in the US as a single agent for KRAS wild type metastatic colorectal cancer after other drugs have failed.[29]

Head and neck cancer

Cetuximab was compared concurrently with RT vs. RT alone in a multinational randomized study of patients with locally advanced head and neck carcinoma.[30] Compared to RT alone the addition of cetuximab significantly improved the duration of local control, (24 vs. 15 months), as well as PFS, (42% vs. 39%), and OS (55% vs. 45%). Importantly comparison of RT alone is no longer the accepted standard for patients with locally advanced head and neck cancer. As the toxicity profile of RT and cetuximab is viewed to be more tolerable compared to chemo-radiotherapy, some may consider it to be more of a substitute for chemo-radiotherapy particularly in the treatment of elderly patients. Current data does not support the use of cetuximab in combination with platinum and radiation therapy. Randomized trials are currently underway to evaluate this combination therapy.

Panitumumab is fully human monoclonal antibodies specific for the extra cellular domain of EGFR.

Cetuximab has shown benefit in patients with metastatic squamous cell carcinoma of the head and neck with combined cisplatin based chemotherapy.[31] In a randomized phase III trial involving 442 patients with recurrent or metastatic head and neck squamous cell carcinoma patients assigned to first line platinum chemotherapy with or without cetuximab. The addition of cetuximab to chemotherapy significantly prolonged the median PFS and OS (5.6 and 10.1 month vs. 3.3 and 7.4 months respectively).[32] Common side effects of cetuximab include acneiform rash, hypomagnesemia, fever, and gastrointestinal symptoms.

Bevacizumab

Bevacizumab is a humanized murine monoclonal antibody that targets vascular endothelial **growth factor receptor A (VEGF)**. VEGF is an important cell specific mitogen that regulates vascular proliferation and permeability. It also functions as anti apoptotic factor for newly formed blood vessels. (33). The antibody targets the process of angiogenesis and the acquisition of new blood vessels by the tumor.

Colorectal cancer

Addition of bevacizumab to a variety of first line regimens used for metastatic colorectal cancer improves outcome. In a randomized phase II trial previously untreated patients were assigned to **bolus irinotecan, fluorouracil (IFL)** with or without bevacizumab. Response rates were higher with bevacizumab and it prolonged median survival by 4 months.[34] Similar results were seen in a phase III trials of bevacizumab in combination with **FOLFOX (5-FU, Leucovorin, and Oxaliplatin)** for first line treatment in metastatic CRC[35] Bevacizumab is active in first line metastatic CRC in combination with oxaliplatin and irinotecan based regimens.[36]

Non squamous non small cell lung cancer (NSCLC)

The initial phase II study investigating a combination of paclitaxel and carboplatin with or without bevacizumab raised safety concerns. Patients with squamous cell histology had higher incidences of fatal pulmonary hemorrhage (~30%). Other risk factors were cavitary lesions, hemoptysis, and brain metastases.[37]

A pivotal phase III trial conducted by **Eastern Cooperative Oncology Group (ECOG 4599)** included 878 previously untreated NSCLC. They were randomized to carboplatin and paclitaxel given every 21 days for six cycles vs. the same doublet combination with bevacizumab. Patients with squamous cell carcinoma, hemoptysis, or history of brain metastases were excluded to minimize the risk of pulmonary or intracerebral hemorrhage. Patients receiving chemotherapy plus bevacizumab had a significant increase in the objective response rate, (35% vs. 15%,) with an overall survival of 12.3 months vs. 10.3 month. One year and two years survival were 51% vs. 44% and 53% vs. 50% respectively.[38] The bevacizumab containing regimen was generally well tolerated. In a second trial conducted in Europe, there was a benefit in terms of PFS however there was no significant difference in OS between treatment arms.[39]

Metastatic Breast Cancer (MBC)

Bevacizumab is FDA approved for breast cancer that does not over express Her2. In the ECOG 2100 trial, 722 women with no prior treatment for MBC were randomly assigned to bevacizumab and paclitaxel or paclitaxel alone.[40] Bevacizumab combined with paclitaxel significantly increased the response rate 37% vs. 21%. and PFS (11.8 months from 5.9 months). In a similar trial the combination of bevacizumab and docetaxel was found to be more beneficial.[41] Pooled analysis from these trials show improvement in PFS but no improvement in OS.

Recurrent Malignant Gliomas (GBM)

Bevacizumab has demonstrated significant clinical activity in phase II single arm studies, both as single agent and when given with irinotecan to patients with grade 3 and grade 4 malignant GBM. The most extensive experience with bevacizumab comes from a randomized non-comparative phase II trial in which 167 patients with recurrent GBM were randomly assigned to bevacizumab either as a single agent or in conjunction with irinotecan.[42] Treatment cycles where repeated every two weeks. All patients received prior chemotherapy with temozolomide. In this trial the objective response rate with bevacizumab alone or with combination with irinotecan was 28% vs.38% respectively and the six month PFS rates and OS were 43% and 53%, 9.2 months and 8.7 months respectively. Treatment with bevacizumab or bevacizumab plus irinotecan was generally well tolerated and toxicity was limited to that expected with these agents.[43]

Metastatic Renal Cell Carcinoma

In a randomized phase II trial single agent bevacizumab improved PFS in patients with advanced renal cell cancer who progressed after immunotherapy.[44]

Two phase III trials have had similar results demonstrating improvement in PFS with the use of bevacizumab plus interferon alpha compared to Interferon alpha alone. [45, 46] Both of these trials excluded patients with brain metastases because of concern for intracranial hemorrhage. The FDA approved avastin for use in combination with Interferon alpha for the treatment of patients with metastatic renal cell carcinoma.

Avastin may have serious side effects including bleeding, thromboses, hypertension, and proteinuria,

Alemtuzumab

Alemtuzumab targets CD-52 and is approved for the treatment of refractory CLL, although it has not been compared with Fludarabine based regimens. Both Alemtuzumab and Fludarabine based therapy have demonstrated superior response rates compared to Chlorambucil based therapy alone. Alemtuzumab alone results in an overall response and complete response rates of approximately 83% and 24% respectively.

In a phase III trial, 297 previously untreated and symptomatic patients with RAI stage I-IV CLL were randomly treated to Alemtuzumab or Chlorambucil.[47] At follow up of 25 months patients treated with alemtuzumab had a higher overall response rate 83% vs. 55% and PFS was 15 month vs. 12 months. On subset analysis higher response rates were seen in high risk patients. The study was not powered to find an OS difference.

Alemtuzumab related toxicity include, lymphopenia, leukopenia, high rate of febrile neutropenia as well as infusion related hypotension, fever, dyspnea, bronchospasm, rash, rarely pulmonary infiltrates, ARDS, and cardiac arrest.

Conclusion

Monoclonal antibodies have been among the most important additions to the therapeutic portfolio of malignant disorders. In most circumstances the effect seems greatest when combined with cytotoxic agents. Several questions remain unanswered including the role of these agents both in mono and combined therapy, duration of use, and the challenge of limiting toxicity. Ongoing and future clinical trials will help define the role of these agents in the treatment of cancer.

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