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Monoclonal antibody therapy

Deirdre O'Mahony and Michael R. Bishop

Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

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1. ABSTRACT

The concept of targeted therapy was conceived through increased understanding of the biological pathways involved in the pathogenesis of cancer and subsequently identification of the most appropriate antigens to target. Monoclonal antibody therapy harnesses host defense mechanisms through activation of the antibody dependent cytotoxic pathway and complement mediated cytotoxicity. However, these two processes alone do not explain the therapeutic efficacy of antibody therapy; they also act by apoptotic signaling and growth inhibitory pathways. Conjugation of monoclonal antibody therapy, with radionuclides or toxins, offers more therapeutic approaches. Initial data demonstrates efficacy of single agent use, although combination therapy appears potentially more

beneficial. Monoclonal antibody therapy is having a significant impact on many disease processes, particularly malignancies of solid and hematological origin. In this article, we shall review and discuss the monoclonal antibodies approved by the US Food and Drug Administration (FDA). in the management of cancer.

2. INTRODUCTION

Many of the biochemical and molecular changes that occur in malignancy are being better defined. As these processes are elucidated, potential targets for new therapeutic strategies are identified. The potential to use our host immune system more efficiently has led to research into the development of monoclonal antibody therapy. Klinmann discovered it was possible to produce monoclonal antibodies against any antigen through their murine transfection studies in 1976 (1). Kohler and Milstein were able to demonstrate that antibody cells from a murine spleen could be immortally fused with myeloma cells. These fused cells were called hybridomas, with the potential to produce endless supplies of antibody (2). The first successful use of monoclonal antibody therapy in humans was in 1982, in a patient with a B-cell lymphoma who achieved a 7 yr remission (3). Custom made monoclonal antibodies were designed against the clonal idiotype in each case. However, the ideal therapy requires an ideal target. Certain favorable target characteristics include that it is homogenously expressed by tumor cells, it is not expressed by normal tissues, it is not shed nor secreted into the circulation, and it has little or no soluble form and is easily accessible to the monoclonal antibody.

Early antibody constructs were murine in origin, and as such were highly immunogenic, limiting their use. The formation of human anti-mouse antibody (HAMA). altered the pharmacokinetic profile of the monoclonal antibody therapy, increasing drug clearance which may interfere with subsequent drug administration. Genetic engineering has enabled the development of humanized antibodies. Chimeric antibodies are 65-90% human and consist of the murine variable regions, necessary for antigen recognition. The constant domains of the protein are derived from human isotypes. Humanized antibodies are 95% human; they are engineered by grafting the hypervariable region, or complementarity determining regions of the murine antibody onto a human antibody backbone. Fully human antibodies may be produced from genetically engineered transgenic mice or the generation of synthetic human antibody libraries. These genetically engineered monoclonal antibodies have variable rates of clearance.

Unconjugated antibodies mediate their effects via recruitment and activation of effector cells by antibody-dependent cellular cytotoxicity, by complement dependent cytotoxicity, by blocking of receptor ligand interactions or by induction of apoptosis. Conjugated antibodies may deliver agents, such as radio-isotopes, toxins or drugs that all have additional cytotoxic effects, to the tumor cells. Ionizing radiation is delivered by radio-immunoconjugates to site of disease. Toxins such as Pseudomonas toxin may be delivered to tumor cells attached to monoclonal antibodies, after binding and internalization in the cell, these toxins disrupt protein synthesis. Drugs such as calicheamicin attached to monoclonal antibodies are internalized and result in DNA damage and subsequent apoptosis.

3. HEMATOLOGICAL MALIGNANCIES

3.1. Rituximab (Rituxan ™, IDEC Pharmaceuticals, San Diego, CA).

3.1.1. General Principles

The CD20 antigen is a suitable target for immunotherapy of non-Hodgkin's lymphoma (NHL). for many reasons. The CD20 antigen is expressed by all cells of the B cell lineage, including more than 95% of B-cell lymphoma cells, but it is not expressed on early lymphocyte progenitor cells. CD20 plays a functional role in B-cell function and its expression is stable, without modulation or internalization. Rituximab is a chimeric antibody produced by combining the murine variable regions from the anti-CD20 murine monoclonal antibody ibritumomab with human IgG1 constant regions via applications of recombinant DNA technology. Similar to other monoclonal antibodies, it induces complement-mediated cytotoxicity (CDC). and antibody dependent cell mediated cytotoxicity (ADCC). as well as direct effects through binding of CD20 (4). Direct CD 20 mediated effects include inhibition of proliferation, induction of apoptosis and sensitization of the lymphoma cells to the effects of chemotherapy (5,6).

3.1.2. Clinical Trials in Low-grade Lymphomas: Monotherapy, Re-treatment and Combination Therapy

Clinical trials with rituximab have been reported using single doses from 10 to 500 mg/m^2 and multiple doses of up to four times of 375mg/m^2 weekly (7,8). Initial trials in patients with refractory and relapsed low-grade NHL resulted in response rates of approximately 50%. In 1998 the FDA approved rituximab as the first monoclonal antibody for the treatment of cancer, based on the pivotal trial of 166 patients with low-grade NHL that had progressed after prior chemotherapy (9). This study established the safety and efficacy of rituximab monotherapy in relapsed and refractory low-grade NHL. It demonstrated an overall response rate of approximately 48% with 42% partial remissions (CR). and 6% complete remissions (CR). The median duration of response was 13.2 months with a small percentage of patients remaining in continuous unmaintained remission for more than 5 years. Shortly after the study was reported an International Workshop for standardization of response criteria in NHL concluded that some of the criteria commonly used to define response were inappropriate (10). When the new criteria was applied an overall response rate of 62% with a CR of 32% was obtained. Serum levels of rituximab were typically elevated for 3-6 months following treatment in those who responded to therapy (11). The relationship between serum levels of rituximab and tumor response has also been demonstrated in patients with diffuse large B-cell NHL (12).

The safety and efficacy of re-treatment with rituximab was reported by Davis in a trial of 60 NHL

patients who had relapsed at least 6 months following prior rituximab therapy (13). Administration of a further 4 week course of rituximab led to response rates of 40% and the responses were sometimes greater and more durable. Median time to progression in responders and median duration of response had not yet been reached at the time the paper went to publication. However Kaplan-Meier estimated median time to progression in responders and median duration of response were 17.8 months (range: 5.4 - 26.6 months). and 16.3 months (range: 3.7 - 25.1 months)., respectively, which were longer than the patients' median durations of response achieved from their prior course of rituximab. The type, frequency and severity of adverse events were not different from those previously reported. No patient developed human anti-chimeric antibodies (HACA). This resulted in further trials examining the role of maintenance therapy. The Swiss Group for Clinical Cancer Research (SAKK). trial studied the extended use of rituximab as maintenance therapy in 202 previously untreated low-grade NHL patients. Patients initially received standard rituximab, and the 151 responders were then randomized to either observation or to receive additional single-agent rituximab at a dose of 375 mg/m^2 that was repeated at 3, 5, 7 and 9 months (14). Among the 46% of patients who had exhibited a response at 12 weeks after starting therapy, on further follow-up at 1 year 80% of the rituximab maintenance arm were still in remission in comparison to only 56% in the standard arm ($p = 0.01$). At a median follow-up of 3 years the use of additional rituximab was associated with a longer duration of remission 23 months versus 12 months ($p = 0.02$).

Rituximab monotherapy has been investigated as an initial form of therapy for low-grade NHL. These studies confirmed that rituximab was effective in this setting, but the response rates were found to be similar to those in patients who relapsed following chemotherapy (15,16). Hainsworth reported that in 62 evaluable patients with previously untreated stage II-IV low grade NHL, rituximab is active and well tolerated (15). Forty-five percent of patients had objective responses (PR = 24 and CR = 4)., while 47% of patients had minor response or stable disease. This study included re-treatment with rituximab after 6 months for all patients who had not progressed. The median progression free survival had still not been reached at a median follow-up of 15 months.

Reports on the use of rituximab in combination with chemotherapy is increasing due to its excellent safety profile, lack of overlapping toxicities, and its potential to sensitize cells to chemotherapy. The greatest synergy is seen with the anthracycline doxorubicin. Czuczman reported the treatment of patients with low-grade NHL with CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone). plus rituximab (CHOP- R). combination (17). The CHOP-R combination was associated with a response rate of 95%, including 58% CR. The median progression free survival had not yet been reached after a median follow-up of 5.5 years with the longest still in remission 7 years later. One study demonstrated a response rate of 90% among 39 patients when treated with a combination of fludarabine and rituximab (18). The median progression free survival had not yet been reached after 1.5 years of follow-up. Cabanillas reported on a randomized, controlled trial of 134 patients with untreated low-grade NHL comparing the combination of fludarabine, mitoxantrone, dexamethasone (FMD). plus rituximab administered for 6 months to FMD alone. A molecular complete remissions was achieved in 90% of the patients receiving FMD-R compared to 67% for FMD alone (19).

3.1.3. Use in Other Lymphomas

Rituximab has been studied in other B-cell lymphomas most prominently in patients with intermediate-grade (e.g. diffuse large B-cell). NHL. Vose reported on one of the first studies of rituximab in combination with CHOP in the treatment of intermediate-grade NHL (20). In this study, 33 previously untreated NHL patients received rituximab (day 1). and CHOP (day 3). on a 21 day cycle for a total of 6 cycles. The overall response rate for 31 evaluable patients was 97%, with 19 patients (61%). achieving a CR and 11 (35%). achieving a PR. Of 13 patients who were bcl-2 positive at baseline, 11 were bcl-2 negative in peripheral blood and bone marrow after treatment. In a randomized phase III study, the Groupe d'Etude Des Lymphomes de L'Adulte (GELA). compared the efficacy and tolerability of CHOP-R with those of CHOP alone in elderly (age > 60 years). with previously untreated diffuse large B-cell NHL. The primary end point of this study was survival. The published results demonstrated that the combination therapy was significantly superior, complete response rates of 76% versus 60% ($p<0.01$). and Kaplan-Meier estimates of 1year overall survival 83% v 68% ($p<0.01$). (21). Rituximab has been combined with other chemotherapy regimens such as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin). and MACOP-B (methotrexate/leucovorin, doxorubicin, cyclophosphamide, vincristine and bleomycin). with high rates of durable complete remissions in patients with intermediate-grade NHL (22,23).

3.1.4. Maintenance Therapy

Maintenance therapy using rituximab is currently under consideration as a means of prolonging remission in patients with low-grade NHL. A phase II trial using rituximab as first-line therapy followed by maintenance treatment was carried out in patients with previously untreated indolent non-Hodgkin's lymphoma (15). The overall response rate improved from 47% (7% complete response). after initial treatment to 73% (37% complete response). after maintenance treatment; median progression-free survival was 37 months. The toxicity of maintenance rituximab has been minimal in all trials to date. Although prolongation of progression-free survival has been shown in all completed trials, multiple other questions regarding maintenance rituximab are being addressed in ongoing trials. These include optimum schedule/duration, use after initial chemotherapy/rituximab combinations, efficacy versus re-treatment at progression, and efficacy in other B-cell neoplasms.

3.1.5. Potential Toxicities

Rituximab is generally well tolerated; mild infusion reactions are common such as fevers, chills, chest

pain, back pain, bronchospasm and hypotension. These usually occur within 30minutes to 2 hours of the infusion. They occur in 65% to 80% of patients during the first infusion but in 35-40% of subsequent infusions. Occasionally rituximab may be associated with tumor lysis syndrome. Hematological toxicities are uncommon but mild leucopenia and anemia may occur Transient thrombocytopenia may occur Arrhythmias have been documented during clinical trials.

3.2. Gemtuzumab Ozogamicin (CMA-676, Mylotarg™, Wyeth Laboatories, Philadelphia, PA).

3.2.1. General Principles

The CD33 antigen is expressed on most hematopoietic stem cells, on both mature immature myeloid cells, on erythroid, megakaryocytic and multipotent progenitors (24). It is also expressed by the majority of blasts in acute myelogenous leukemia (AML). patients. As CD33 is not widely expressed by cells outside the hematopoietic system, it represents an attractive target for monoclonal based therapy. Several approaches to anti-CD33 monoclonal antibody have been attempted including naked antibody, radio-immunoconjugates and immunotoxin conjugates. Gemtuzumab ozogamicin, has been the most successful. It is a humanized murine monoclonal antibody that targets the CD33 antigen and is chemically linked to calicheamicin, an enedieyne anti-tumor antibiotic that results in DNA cleavage and apoptosis (25). It was approved by the FDA in May, 2000 under the accelerated approval regulations for the treatment of CD33-positive AML patients in first relapse who are 60 years or older and not considered candidates for chemotherapy (26).

3.2.2. Pre-Clinical Data

van Der Velden demonstrated the targeting of gemtuzumab ozogamicin in AML, with rapid internalization of the compound and subsequent induction of cell death both *in vivo* and *in vitro* (27). Amico also performed some pre-clinical work investigating the various effects on different human AML cell lines. They demonstrated 3 different responses on exposure to the drug: G2 arrest followed by apoptosis, G2 arrest with little apoptosis, and resistance to gemtuzumab ozogamicin. It was suggested that the ATM/ATR-chk1/chk2 pathway is important in mediating the cellular responses to mylotarg (28).

3.2.3. Clinical Trials

In a single phase I dose escalation study 40 patients were treated with refractory or relapsed CD33+ AML with single agent gemtuzumab ozogamicin in doses ranging from 0.25 - 9.0 mg/m^2 (26). Eighteen patients had prior stem cell transplant. Eight patients (20%). had a reduction in peripheral blood and/or bone marrow blast counts less than 5%. Dose limiting toxicity was neutropenia and persistent thrombocytopenia. However, there appeared a cohort of patients who had apparent blast clearance but persistent thrombocytopenia (<100 x 10^9/L, independent of platelet transfusion). leading to the proposal of a new category of responses termed complete remission without platelet recovery (CRp). The recommended study dose for phase II was 9.0mg/m^2 intravenously over 2 hours for 2 doses with a 14 day interval. Three open label, multi-center phase II trials were initiated (29). A total of 142 patients were enrolled, median age of 61years (range: 22-84 years)., the initial overall response rate (both CR and CRp). was 29% with a median time to remission of 60 days. All patients received the first dose, 109 patients (77%). received a second and only 5 (3%). received a third dose. Infusion related adverse events, grade 3 or 4, occurred in 34% of patients after the first dose of gemtuzumab ozogamicin and in 12% of patients with the second dose. Grade 3 or 4 neutropenia and thrombocytopenia occurred in 97% and 99% of patients respectively. It was on the basis of these data that the FDA approved gemtuzumab ozogamicin for clinical use.

Updates on the early data demonstrate that examining a total of 277 AML patients who received gemtuzumab ozogamicin, a CR of 13 % was identified as was a similar rate of CRp (30). The median remission free survival for all patients achieving remission was 5.3 months. The results of another phase II study have been compared with results from matched patients who received high-dose cytarabine (HIDAC). based combination therapy for AML in first recurrence (31). The study included 128 AML patients; the overall response rate was 38% with gemtuzumab ozogamicin and 40% with HIDAC. The data suggested a correlation between short CR duration and better response to gemtuzumab ozogamicin compared with HIDAC. It was associated with a higher remission rates if the duration of first CR was 3.0-10.5 months, but HIDAC was superior if the duration of CR was greater than19 months (31).

3.2.4. Future Role

Gemtuzumab ozogamicin is currently being evaluated in combination with conventional chemotherapy and stem cell transplant protocols. A pilot study of gemtuzumab ozogamicin, idarubicin and cytarabine (GIA). combination demonstrated an overall response rate of 43%. Of the 14 evaluable patients, GIA induced CR in 3 patients and a CRp in 3 patients. The median survival was 8 weeks (range: 2-64 weeks). and the median failure free survival of CR was 27 weeks (range 11-64 weeks). All patients developed grade 3-4 myelosuppression and severe sepsis occurred in 10 patients (71%)., and 2 (14%). patients developed veno-occlusive disease (VOD). (32). Another pilot study in combination with cytarabine and topotecan has been reported in 17 patients , with only 2 patients (12%). achieving a CR with a median survival of 8.2 weeks. 29% developed grade 3/4 liver toxicity and 1 patient (6%). died from VOD (33). Gemtuzumab ozogamicin has also been used with all-trans retinoic acid (ATRA). for acute promyelocytic leukemia, of 19 patients treated 16 of them (84%). achieved a CR, with 14 in molecular CR (34).

3.2.5. Potential Toxicities

Minor infusion related reactions have been documented with gemtuzumab ozogamicin administration; they occur at a frequency of 4-11% and vary from fever, chills to shortness of breath and hypotension. These have been significantly reduced with premedication with anti-histamines and acetaminophen. If severe reactions occur

despite these measures, steroids have been effective in further decreasing the risk of infusion reactions (35). The grade 3-4 toxicities that have been reported with gemtuzumab ozogamicin administration include pancytopenia and hepatotoxicity. In the analysis of 277 patients neutropenia and thrombocytopenia occurred in 98% and 99% respectively. However less than one third of patients experienced grade 3 or 4 infections and only 15% had episodes of bleeding (29,30). Hepatoxicity occurs in 39% of patients treated with gemtuzumab ozogamicin phase II studies, these were transient in the majority of cases. However 7 patients developed VOD, the constellation of fluid retention, tender hepatomegaly and jaundice. There have been no definitive clinical factors to predict the development of VOD after gemtuzumab ozogamicin administration; however, Goldberg retrospectively analyzed 61 patients undergoing myeloablative allogeneic HSCT for AML and a multivariate logistic regression analysis of all patients demonstrated that prior exposure to gemtuzumab ozogamicin is an independent risk factor for VOD development (36). It is believed that the hepatotoxicity is related to toxic damage to the sinusoids with resultant ischemia and necrosis, perhaps related to exposure to calicheamicin, receptor mediated uptake by CD33+ cells in the liver or non-specific uptake of gemtuzumab ozogamicin by the kupffer cells (37).

3.3. Alemtuzumab (Campath-1H ™, Ilex Pharmaceuticals, San Antonio, TX

3.3.1. General Principles

Alemtuzumab is a humanized monoclonal antibody (IgG1). directed against CD52, a non-modulating glycosylated peptide antigen that is expressed on mature B and T lymphocytes, monocytes, and spermatozoa. It is not expressed on hematopoietic stem cells, erythrocytes or platelets. The majority of B-cell lineage neoplasms express the CD52 antigen. Increased expression has been demonstrated particularly on B-cell chronic lymphocytic leukemia (B-CLL). and T-prolymphocytic leukemia (T-PLL). As a member of the IgG1 class of immunoglobulins, it is a powerful activator of both complement and antibody dependent cytotoxicity. Although both rituximab and alemtuzumab carry the same IgG1 Fc region they differ in their ability to activate human complement (38). Complement activity is not completely necessary for the depletion of CD52 positive cells *in vivo* (39). *In-vitro* data demonstrates that cross linking CD52 with the humanized monoclonal antibody induces growth inhibition and apoptosis (40). However, the effector mechanisms of alemtuzumab are not completely understood.

3.3.2. Clinical Trials

In 1992, results from a phase II multi-center study of alemtuzumab in previously treated low-grade NHL demonstrated limited activity (14% PR). but lymphoma cells were rapidly eliminated from the blood in 94% of patients and CR in bone marrow was attained in 32% (41). This led to pilot studies in B-CLL, as it is a disease characterized by malignant lymphocytosis. Results reported, by Keating were pivotal in the FDA approval of Alemtuzumab in the treatment of fludarabine refractory or relapsed B-CLL. This phase II study examined the safety and clinical efficacy of intravenous Campath-1H. Of 93 patients from 21 centers, an overall response rate of 33% was noted and a CR of 2%. Median time to progression was 9.5 months for responders, 19 responders survived more than 21 months. Alemtuzumab was administered at 30mg three times weekly for a maximum of 12 weeks (42). Blood and bone marrow responded better than bulky disease. Rai also reported results from their phase II study of safety and efficacy of intravenous alemtuzumab. In 24 patients , there was 33% overall response rate (all PR)., median duration of response was 15.4 months (range: 4.6 – 38+ months). and the median survival time was 35.8 months (range: 8.8 - 47.1 months). (43). Alemtuzumab has also been studied as first line therapy in the management of B-CLL. Osterborg reported an overall response rate of 89% and a CR of 33% with the use of alemtuzumab intravenously (30 mg, three times weekly). in chemo-naïve patients (44). Lundin reported overall response rates of 87% in 38 evaluable patients, including CR in 19% of patients, giving alemtuzumab by subcutaneous administration (45).

The use of alemtuzumab in other settings is also under study. Researchers at the MD Anderson Cancer Center in Houston experience reported in a retrospective analysis on 76 patients with T-PLL who received intravenous alemtuzumab. An objective overall response rate of 51% with a 39.5% CR was identified. The median duration of CR was 8.7 months (range: 0.13 – 44.4 months)., and the median time to progression was 4.5 months (range 0.1-45.4 months). (46). Uppenkammp investigated alemtuzumab in patients with relapsed high and low grade NHL, it appeared that only patients with low grade NHL responded to alemtuzumab (47).

The combination of alemtuzumab with other therapies had demonstrated clinical benefit. The combination of alemtuzumab and rituximab was reported in 48 patients with relapsed and refractory lymphoid malignancies including CLL, T-PLL, mantle cell NHL, and NHL after Richter's transformation; however, responses were only noted in the CLL or T-PLL subgroups. An overall response rate of 52% was documented, in the CLL subgroup 20 of 32 patients responded while there were 4 responses in 9 patients with CLL/T-PLL (48). The combination of alemtuzumab and Fludarabine has been shown to induce responses in patients previously refractory to either treatment, causes responses in 5 out of 6 patients in one particular trial (49). It is also being studied in the transplant setting. Alemtuzumab has been efficacious for controlling graft-versus-host disease after allogeneic HSCT (50).

3.3.3. Potential Toxicities

The most common toxicities associated with alemtuzumab administration are infusion related, such as rigors, fever, urticaria and hypotension, which are mediated by cytokine release. Engagement of the FCγR receptor on natural killer cells leads to the transcription of interferon-γ, tissue necrosis factor-α and IL-6 (51). Pre-medication with

acetaminophen and diphenhydramine is usually administered to lessen the severity of infusion reactions. Profound lymphopenia and reduced cell-mediated immunity follow Alemtuzumab therapy. Most patients have no circulating lymphocytes by week 4 of therapy. Studies demonstrate cytomegalovirus (CMV). reactivation from 16-33% of patients treated with alemtuzumab. Reactivation of CMV is described in most alemtuzumab studies, and monitoring of peripheral blood for CMV by polymerase chain reactions has become routine. Pre-emptive introduction of ganciclovir, at the time of CMV antigen positivity in the peripheral blood, before the onset of clinically overt disease, has been successful (52). Reactivation of latent herpes and Varicella zoster viruses occur commonly, therefore warranting prophylactic antiviral therapy. Opportunistic infections may also occur; Rai reported Pneumocystis carnii pneumonia in 4 of 93 patients, none of whom were receiving prophylaxis (43). Hematologic toxicity includes grade 4 neutropenia in 21% of patients at a median of 4 weeks (45). The mechanism of neutropenia is unknown, however was responsive to colony stimulating factors.

3.4. Ibritumomab Tiuxetan (Zevalin™, IDEC Pharmaceuticals, San Diego, CA).

3.4.1. General Principles

Radio-immunotherapy combines biologic and radiolytic mechanisms to target and destroy tumor cells. It is a process whereby a radionuclide is conjugated to a monoclonal antibody directed to a specific antigen expressed on tumor cells, making it possible to target radiation to the tumor cells minimizing the toxicity to normal tissue. Its mechanisms include antibody dependent cellular cytotoxicity, complement mediated cytotoxicity, induction of apoptosis and direct cytotoxic ionizing radiation. Tumor cells within close proximity and inaccessible to antibody or those with insufficient antigen expression may be affected by a "bystander" or "crossfire" effect. The choice of radionuclide varies depending on the clinical situation (53). Yittrium 90 (^{90}Y). is a pure β emitting isotope, it can deliver more energy and a greater path length than iodine 131 (131I). 5mm versus 0.8mm, and it has a favorable half-life (T1/2). However as it is a pure β emitting isotope it cannot be used for imaging, therefore the gamma emitter indium-111 is necessary for dosimetry and imaging.

Ibritumomab tiuxetan is composed of the murine parent of rituximab, ibritumomab (Y2B8)., an IgG1 antibody with tiuxetan (MX-DTPA)., which functions as a bifunctional chelator forming a strong thiourea covalent bond with stable retention of ^{90}Y (54). In February 2002, ibritumomab tiuxetan was the first radio-immunoconjugate to be FDA approved for the treatment of relapsed or refractory follicular/low grade or transformed lymphoma. Wiseman performed a phase I/II study to investigate safety and efficacy of 90Y-ibritumomab tiuxetan. It was devised to determine the rituximab dose needed to clear peripheral blood B cells and optimize distribution of ibritumomab tiuxetan, to determine the maximum tolerated dose (MTD). of ibritumomab tiuxetan and identify the absorbed radiation dose to normal organs and bone marrow (55). The clinically defined MTD was 15 MBq/kg (0.4 mCi/kg). in patients with normal platelet counts and 11MBq/kg (0.3 mCi/kg). in patients with mild thrombocytopenia (100,000 - 149,000). The only significant toxicities were hematological, although these were transient, reversible and dependent on bone marrow reserve in heavily pre-treated patients. It has been shown that the duration of thrombocytopenia is directly related to the ibritumomab tiuxetan dose, and that weight adjusted dosing (MBq/kg). predicted the outcome better than the body surface area adjusted dosing (MBq/m2). or the actual dose (total MBq).

3.4.2. Clinical Trials

In the initial phase I/II trial the overall response rate in 32 patients with follicular (low-grade). NHL was 82%. There was a CR rate of 26% (56). In 14 patients with intermediate-grade NHL the response rate was 43% with 29% CRs. The median time to progression was 12.9 months, and the response duration was 12.9 months. These promising data lead to the direct comparison of ibritumomab tiuxetan and rituximab (57). A phase III, multi-institutional randomized study enrolled 143 patients with relapsed or refractory low grade, follicular or transformed B cell NHL. Despite comparable characteristics between the 2 groups, ^{90}Y-Zevalin was significantly more active with an overall response rate of 80% versus 56% ($p = 0.002$)., a complete response rate of 30% versus 16% ($p = 0.04$). Durable responses of greater than 6 months were achieved in 62% of patients treated with ibritumomab tiuxetan versus 47% of those treated with Rituximab ($p = 0.03$). Time to disease progression was 11.2% versus 10.1 months ($p = 0.173$). in all patients. Reversible immunosuppression was the primary toxicity; median neutrophil and platelet nadirs occurred approximately 6-7 weeks post-treatment with a duration of approximately 2 weeks. The ibritumomab tiuxetan group did require more hematological support with colony stimulating factors and blood bank support.

As rituximab therapy has now an established role in the treatment of NHL expressing CD20, Witzig studied whether NHL patients refractory to rituximab can subsequently respond to ibritumomab tiuxetan considering the core of both therapies is the anti-CD20 monoclonal antibody (58). Refractory was defined as no objective response to rituximab 375mg/m^2 every week for 4 weeks or time to progression (TTP). $\leq$ 6 months. The overall response rate in 54 patients with follicular NHL was 74% (15% CR, 59% PR).; however, there was some tumor shrinkage in 94% of patients. The Kaplan-Meier estimated TTP was 6.8 months for all patients (range: 1.1 - 25.9 months). Grade 4 toxicity included neutropenia (35%)., thrombocytopenia (9%). and anemia (4%).

A report on the long-term follow-up of a phase I/II study of ibritumomab tiuxetan in 51 patients for relapsed or refractory B-cell NHL demonstrated overall response rates of 73% in all patients: 51% CR/Cru, 22% PR (59). In the follicular NHL group there was an overall response rate of 85% - 57% CR/Cru, 27% PR. The median time to progression was 12.6 months; however, in the patients with CR the time to progression has been 28.3

months. 9 patients have time to progression greater than 3 years. Two patients (4%). developed myelodysplastic syndrome 2 to 3 years after ibritumomab tiuxetan, but these patients were heavily pre-treated (median of 4 or 5 chemotherapy regimens). The incidence of HAMA was 2%.

3.4.3. Potential Toxicities

Integrated safety data demonstrate that the primary toxicity of ibritumomab tiuxetan is hematologic (60). The most common side effect is reversible, delayed myelosuppression, the nadir occurring 7-9 weeks following therapy. Grade 3 or 4 neutropenia occurring in 57% and grade 3 or 4 thrombocytopenia occurred in 61%. The rate and duration of hematological toxicity did not correlate with dosimetric measurements of ibritumomab tiuxetan. It was related to the patient bone marrow reserve and history of prior chemotherapy. Non-hematologic toxicities include asthenia, nausea, vomiting, infection, chills, fever and abdominal pain. The reported incidence of HAMA/HACA is 2% following therapy with ibritumomab tiuxetan. Other potential concerns are the risk for secondary malignancies, particularly chemotherapy related acute myelogenous leukemia. It has only been identified in 10 of 770 patients (1.3%). of patient s treated with ibritumomab tiuxetan. All 10 patients had received prior chemotherapy (61). But this may increase with longer follow-up. Ibritumomab tiuxetan is an effective safe therapy for relapsed, refractory low grade, follicular or transformed B-cell NHL.

3.5. Tositumomab (Bexxar™, Corixa, Seattle, WA, GlaxoSmithKline, Philadelphia, PA).

3.5.1. General Principles

Tositumomab is composed of an anti-CD20 monoclonal antibody linked to ^{131}I. Tositumomab is a murine IgG2a anti-CD20 monoclonal antibody. The high energy β emissions of ^{131}I are only cytotoxic over median distance of 8mm but this limits toxicity to normal surrounding tissue. The γ emissions of 131I increase the whole body dose and require shielding of hospital personnel and restriction following discharge but dosimetry can be performed without using a substitute radioisotope. Free ^{131}I in the blood may be taken up by the thyroid, therefore to limit damage the patients must be blocked by supersaturation with potassium iodine solution (SSKI). to patients before and during therapy (53).

3.5.2. Clinical Trials

Stagg and colleagues in a phase I/II study of ^{131}I anti-B1 antibody performed dosimetric studies demonstrating a pre-dose of 475 mg of unlabelled anti-B1 antibody optimized the tumor to total body ratio of radioactivity (62). The maximum tolerated dose of tositumomab for a patient who had not undergone a prior bone marrow transplant was 75 cGy total body dose. In 42 patients an overall response rate of 71% was observed with a median duration of response of 8.9 months. On further analysis a complete response rate of 34%, with a median duration of responses in this subgroup of 18.3 months was identified. As a consequence of the potential for prolonged myelosuppression, patient eligibility for clinical trials dictated less than 25% bone marrow involvement. Vose reported on the first multi-center study of tositumomab that investigated the efficacy, dosimetry, methodology and safety of tositumomab for chemotherapy relapsed/refractory low grade and transformed low grade B cell NHL (63). In all, 47 patients were enrolled onto study and the overall response rate was 57% with a median duration of response of 9.9 months was observed. A CR was seen in 15 patients (32%)., 6 of these patients continue in CR with ongoing duration of responses ranging from 26.9 - 33.8 months.

In a multi-center trial, 60 patients with chemotherapy refractory low-grade or transformed low grade B cell NHL received tositumomab to determine efficacy and toxicity (64). In this population an overall response rate of 65%, complete response rate of 20% was observed, and the median duration of response was 6.5 months. Complete responses were also noted to be durable; the median response duration had not yet been reached in this subgroup. Leonard reported on a large multi-center expanded access study of tositumomab in patients with relapsed or refractory B cell NHL (65). Involving 65 sites, 475 patients were enrolled however only 394 patients were evaluable. The overall response rate was 59% with a median duration of 15 months, of those 26% patients had a CR the median duration was not reached after 9 months. The median time to progression for responders was 18 months.

Tositumomab therapy has also been shown to have high response rates and durable remissions with previously untreated, advanced stage, follicular NHL. Kaminski in a single institution study demonstrated ORR of 95% and CR 75% (66). Of the patients achieving a CR in this study, a significant proportion of them remained in a continuous CR from 30 - 66 months after treatment. After a median follow-up of 5.1 years, the actuarial 5-year progression-free survival for all patients was 59 percent, with a median progression-free survival of 6.1 years. Tositumomab is also a safe and effective therapy for those patients who have failed to respond to rituximab (67). It produced OR in 86% of patients with median progression-free survival for responders was of 24.5 months. Fifty-seven percent of patients achieved CR; the median duration of response for these patients had not yet been reached.

3.5.3. Potential Toxicities

The dose limiting toxicity of tositumomab administration is hematological. The incidence of grade 3 or 4 toxicity is approximately 30-40%. Nadirs occur at weeks 4-6 after treatment with recovery to grade 2 by week 8-9. In the expanded access study, summarizing experience from 425 patients, grade 4 neutropenia occurred in 14% (65). Blood transfusions and colony stimulating factor support was sometimes necessary. Other toxicities include mild infusion reactions; these were more common with the dosimetry infusion than the therapeutic infusions. Fatigue, nausea, anorexia, arthralgia, myalgia, and rash have also been documented as grade 1 and 2 toxicities. All patients are treated with a thyroid blocking agent before and during administration, however elevated thyroid stimulating hormone (TSH). levels were observed in 8.5% of a phase I

study (63). The development of HAMA after of tositumomab administration appears to be less than 10%, but it appears to be dependent on the extent of prior therapy. In one study 63% of previously untreated patients developed HAMA (66). The clinical significance of HAMA / HACA is unclear and it does not appear to have an adverse effect on the patient. Secondary myelodysplastic syndrome / acute myelogenous leukemia has been reported in 19 (3.1%). of 620 heavily pre-treated patients. On retrospective analysis 5 of these patients had evidence of MDS/AML at study entry, 11 of 12 patients had cytogenetic changes in chromosomes 5 and/or 7 consistent with alkylator induced chromosomal damage at time of diagnosis of myelodysplastic syndrome (MDS)./AML. When the newly diagnosed patients treated with Bexxar alone are reviewed, none of 76 patients have developed MDS/AML at a median follow-up of 4.1 years (range: 0.7 - 6.3 years). (68). It is also important that the patients and family are educated with regard to safety measures to take after tositumomab therapy. Avoidance of close contacts for 1 to 2 weeks, no bed sharing for 1-2 weeks, avoidance of long car journeys (>4 hours)., and avoidance of crowded public places for 1 week . In addition, there should be no direct contact with pregnant women or children.

4. SOLID MALIGNANCIES

4.1. Trastuzumab (Herceptin™, Genetech Inc., San Francisco, CA).

4.1.1. General Principles

Human epidermal growth factor receptor-2: HER2 (c-erbB-2/neu; HER2/neu). is a tyrosine kinase membrane receptor which, on activation, induces a phosphorylation cascade in cytoplasmic kinases leading to increased protein transcription and cellular growth. HER2 is now well established as a marker of poor prognosis in breast cancer; its amplification is associated with aggressive tumor behavior and shortened survival. It is seen in approximately 30% of breast cancer patients (69,70). Several pre-clinical experiments demonstrated the aggressiveness of HER2. The introduction of HER2 into non-neoplastic cells causes their malignant transformation (71). Antibodies directed against HER2 can inhibit growth of tumors and of transformed cells that express high levels of this receptor, suggesting that this may be a potential target in breast cancer (72-74). Trastuzumab is a humanized monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor 2 protein. The antibody is an IgG1 kappa that contains human framework regions with complementarity determining regions of a murine antibody (4D5). that binds to HER2.

4.1.2. Clinical Trials in Metastatic Breast Cancer

The pharmacokinetics of trastuzumab was studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10-500 mg once weekly demonstrated dose dependent pharmacokinetics. The half-life averaged 1.7 and 12 days at the 10 mg and 500 mg dose levels, respectively. In studies using a loading dose of 4mg/kg followed by a weekly dose of 2mg/kg, a mean half-life of 5.8 days was observed. One of the first clinical trials of trastuzumab monotherapy in heavily pre-treated women with metastatic breast cancer was reported (75). With reported response rates of 11.6%, it held some promise as a new relatively non-toxic targeted therapy. It eventually became apparent that there were a significant number of women achieving long periods (>6 months). of disease stability (76). Pietras reported *in vitro* data in human breast and ovarian cancer cells demonstrating a synergistic decrease in cell growth when both the anti-p185 antibody and cisplatin are used in combination (77). In addition, the antibody mediated an increased sensitivity to cisplatin in drug resistant ovarian cancer cell lines. Therapy with antibody to the HER2/neu receptor led to a 35-40% reduction in repair of cisplatin–DNA adducts after cisplatin exposure and as a result promoted drug induced killing in target cells. This led to a phase II trial of Herceptin with cisplatin in metastatic breast cancer (78). The response rate was 26%, with a median response duration of 5.3 months. This compared favorably with a RR of 11% with trastuzumab alone and a historical control of 9% with cisplatin alone.

The safety and efficacy of trastuzumab was studied in a randomized, controlled clinical trial in combination with chemotherapy in an open label single agent trial in patients whose breast cancer over-expressed HER2/neu at the 2+ or 3+ level by immunohistochemistry (IHC). using a panel of two antibodies. Slamon reported on the results of a multi-center randomized controlled clinical trial of trastuzumab that included 469 breast cancer patients. Patients with no prior anthracycline exposure received anthracyclines plus cyclophosphamide (AC). alone or in combination with trastuzumab (79). Patients who had been previously treated with anthracyclines received paclitaxel alone or in combination with Trastuzumab. After a 14 month follow-up, addition of trastuzumab to chemotherapy led to a significantly improved time to disease progression (7.8 months vs. 4.6 months, $p = 0.0001$)., overall response rate (50% vs. 32%, $p < 0.0001$). and higher median response duration (9.1 vs. 6.1 months, $p = 0.0002$). After a 29 month follow-up the overall survival remained significantly increased, 25.4 months versus 20.3 months ($p < 0.025$). The most severe adverse event occurring was cardiac dysfunction. Cobleigh reported on an open label trial in 222 patients with metastatic breast cancer receiving trastuzumab alone (80). The overall response rate was 22%, with a median duration of response of 9.1 months and median survival of 13 months. A retrospective analysis of those patients achieving stable disease increased the clinical benefit to 23%. Reanalysis using the fluorescent in-situ hybridization (FISH). assay for HER2/neu demonstrated that the response rate for 3+ patients was 18% while the response rate for 2+ patients was 6%, no patient who was FISH-negative responded to trastuzumab (81). The results generated from these two pivotal trials led to the FDA approval of trastuzumab in the management of metastatic breast cancer in September 1998.

Vogel reported superior results with trastuzumab in patients who are FISH-positive for HER2/neu over-expression (82). In this study patients with either 2+ or 3+

by IHC over-expression were randomized to receive either standard trastuzumab dosing consisting of a 4 mg/kg loading dose and 2 mg/kg weekly thereafter or higher trastuzumab dosing consisting of a 8 mg/kg loading dose and 4 mg/kg weekly thereafter. The overall response rate was 26% (range: 18 - 34%)., when only 3+ over-expression patients were evaluated the response rate was 35% (range: 24 - 48%). No significant differences were noted between the two dose levels. Analysis by FISH was performed and there was a 34% response rate and 48% clinical benefit rate among those patients who were FISH-positive as compared with 7% and 10% in FISH-negative patients.

Numerous combinations of trastuzumab and other chemotherapeutic agents have been reported (83-85). MD Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center in New York examined the response of weekly paclitaxel and trastuzumab in the setting of metastatic breast cancer in those patients whose disease did or did not over-express HER2/neu by IHC (83). Ninety four patients were enrolled, and a response rate of 75% was noted for FISH-positive tumors, while it was 41-46% for tumors that were FISH-negative. Esteva reported response rates of 67% for FISH positive patients treated with the combination of weekly docetaxel and trastuzumab (84). Significant toxicities included epiphora in 93% of patients, 12 patients requiring intervention with canalicular intubation. The clinical efficacy and side effect profile of vinorelbine and trastuzumab was reported by Burstein (85). Overall response rates of 75% were observed. When used as first line agent in metastatic disease it may have a response rate of 84%. In patients receiving it as second or third line the response rate was 60%.

4.1.3. Potential Toxicities

Trastuzumab is generally well tolerated, with the most common adverse events being mild to moderate in severity. Infusion related symptom complex of chills, fever, dyspnea, and bronchospasm is observed in approximately 40% of patients. Nausea, vomiting and tumor related pains are infrequent side effects. The most worrisome adverse event is the potential to develop cardiac dysfunction. In the phase II trial cardiac dysfunction occurred in 26% of patients receiving the trastuzumab and AC combination, 6% of patients with AC alone, 12% receiving paclitaxel and trastuzumab and 2% in those receiving paclitaxel alone (79). Leukopenia, anemia, or thrombocytopenia are extremely rare, unless Trastuzumab is administered in combination with chemotherapy.

4.1.4. Future directions

The use of Trastuzumab in the adjuvant setting is still under investigation. The difficulty with its use in this setting is the risk of cardiotoxicity, as most current adjuvant therapies are built on a core of anthracyclines. In the US there are two trials of the National Surgical Adjuvant Breast and Bowel Project (NSABP). and Inter-Group using sequential doxorubicin and cyclophosphamide followed by paclitaxel and either concomitant or delayed Trastuzumab. The BCIRG also investigates adjuvant therapy with Herceptin, however in combination with docetaxel and carboplatin. The HERA trial is a European study looking at different combination chemotherapy regimens, once completed randomization to sequential Trastuzumab therapy or not. The results of these trials are anxiously awaited to help determine the role of targeted therapy at an earlier stage.

4.2. Bevacizumab (Avastin™, Genetech Inc., San Francisco, CA)

4.2.1. General Principles

Vascular endothelial growth factor (VEGF). is one of many factors involved in regulation of angiogenesis – the formation of new blood vessels – which is of paramount importance in the survival and growth of primary and metastatic tumors. VEGF is not constitutionally expressed in normal colonic epithelium; however it is expressed in approximately 50% of colorectal cancer (86). It is also expressed in breast, ovarian and non-small cell lung cancer. Preclinical data initially implicated VEGF in tumor growth, its transfection into colon cancer cell lines enhanced angiogenesis, tumor growth and metastasis when the cancer cell lines are xenografted into nude mice (87,88). Subsequently, it was demonstrated in the clinical situation that increased expression is correlated with lymph node positivity and distant metastasis in colorectal cancer (89). These findings suggested that VEGF could potentially be an attractive target leading to the development of bevacizumab, a recombinant humanized monoclonal antibody with selectivity against VEGF. Bevacizumab is derived from the murine antibody A.4.6.1, comprises 93% human IgG framework and 7% murine derived antigen-binding regions, the humanization providing a longer half-life and less immunogenicity. The antibody is able to combat endothelial cell mitogenic activity, vascular permeability enhancing activity and angiogenic properties.

4.2.2. Clinical Trials

The initial phase I protocol of bevacizumab enrolled 25 patients with dose escalation from 0.1 - 10.0 mg/kg (90). Disease stabilization was seen in 48% of patients. No grade 3 or 4 toxicity was identified that was directly attributable to therapy. There were 3 episodes of tumor related bleeding. Grade 1 and 2 toxicity included asthenia, nausea and headache. This led to a further phase I study investigating bevacizumab in combination with chemotherapy. Kabbinavar reported on a phase II randomized trial comparing bevacizumab in two dosing schedules of 5mg/kg or 10mg/kg plus 5-fluoruracil (5FU). at 500mg/m^2 plus leucovorin (LV). at 500 mg/m^2 with 5FU/LV alone in patients with metastatic colorectal cancer (91). Both combination therapy arms were associated with superior response rates (17% in the control arm vs. 40% in the low-dose bevacizumab and 24% in the high-dose bevacizumab arm)., longer median time to disease progression (5.2 vs. 9.0 vs. 7.2 months, respectively). and longer median survival (13.8 vs. 21.5 vs. 16.1 months, respectively). Toxicity include diarrhea, stomatitis and leucopenia in all arms, however greater incidences of hemorrhagic complications in the bevacizumab arms. Thrombosis (fatal in one case)., epistaxis, proteinuria and hypertension were all documented with the bevacizumab and chemotherapy arms. These data suggested that possibly

the higher dose of bevacizumab may cause excessive vascular collapse thereby inadvertently limiting chemotherapy delivery to the tumor.

The Eastern Cooperative Oncology Group (ECOG). study performed a phase II trial to study the activity and safety of the combination of irinotecan (125 mg/m^2)., 5FU (500 mg/m^2). and LV (500 mg/m^2). weekly for 4 of 6 weeks plus bevacizumab (10 mg/kg). every 2 weeks (92). It found that the addition of bevacizumab did not increase the incidence of known toxicities related to the chemotherapy and there were no significant bleeding or thrombotic complications. These studies led to the development of the phase III study of bevacizumab plus irinotecan, 5FU and LV (IFL). for metastatic colorectal cancer that were recently reported. Hurwitz demonstrated that the addition of bevacizumab to fluorouracil based combination chemotherapy results in statistically significant median durations of survival (20.3 months vs. 15.6 months, $p < 0.0001$). (93). As compared with IFL alone, the combination of bevacizumab and IFL increased the overall response rate from 34.8% to 44.8%, and increased the median duration of response from 7.1 to 10.4 months. A further ECOG study, E3200, shall evaluate the addition of bevacizumab to oxaliplatin, leucovorin, and 5-flourouracil (FLOFOX4). An interim toxicity analysis of E3200 on 757 patients was presented at the 2004 Annual Meeting of American Society of Clinical Oncology; the addition of bevacizumab to the FOLFOX4 regimen did not substantially alter the regimen's toxicity profile (94). The role of bevacizumab in the management of early cancers remains to be elucidated, as does its role in conjunction with radiation remains to be answered.

4.2.3. Potential Toxicities

The optimal dose of bevacizumab has yet to be established, phase I and II data demonstrated a benefit for 5 mg/kg every 2 weeks; however, E3200 is using a dose of 10 mg/kg. When bevacizumab was combined with IFL, grade 3 hypertension was identified in 11% of patients; there was no evidence of increased thrombotic or bleeding episodes. However, gastrointestinal perforation occurred in 6 patients on IFL and bevacizumab (1.5%)., one patient dying as a result of this complication. It was postulated that VEGF inhibitors inhibit dermal wound angiogenesis. Increased apoptosis of endothelial cells by bevacizumab leads to exposure of sub-endothelial cells thereby triggering a coagulation cascade, potentially increasing the bleeding and thrombotic risk. However, these events may in part be related to the underlying malignancy.

4.3. Cetuximab (IMC-225; Erbitux™, Bristol Myers Squibb, Princeton, NJ)

4.3.1. General Principles

Cetuximab is a chimeric IgG1 monoclonal antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR). competitively inhibiting EGF binding and thus its action. Activation of EGFR leads to a cascade of functions such as proliferation, differentiation, survival and angiogenesis, all functions necessary in the evolution of malignancy. Over-expression of EGFR is frequently identified in solid tumors, such as colorectal, breast, lung, head and neck, glioblastoma, bladder, ovarian cancer and many more (95). Over-expression of EGFR has been reported in 60-75% of colorectal cancers and is associated with a poor prognosis (96). Therefore it seemed prudent to develop a therapy to target this receptor. There are many potential mechanisms for targeting the EGFR, such as monoclonal antibody therapy interfering with receptor signal, antisense oligonucleotides or ribozymes that block receptor translation, monoclonals serving as carriers of toxins or prodrugs and the prevention of receptor transit to the cell surface. Blockade of EGFR by cetuximab has been shown to inhibit the growth of colon cancer cell lines *in vitro* and of xenografts by disrupting the EGFR mediated signal transduction both as a single agent and in combination with chemotherapy (97). The combination of chemotherapy and cetuximab has demonstrated significantly enhanced tumor activity. It demonstrates additivity rather than synergy with chemotherapy. Optimal tumor cell inhibition is achieved when the EGFR is saturated by the monoclonal antibody. This led to the dosing recommendation in patients of a loading dose of 400 mg/m^2 followed by weekly administration of maintenance of 250 mg/m^2.

4.3.2. Clinical Trials

The first clinical trial of cetuximab for colon cancer was performed in heavily pre-treated patients with EGFR positive patients (98). As patients exhibited major responses to treatment this led to the development of phase II studies (99,100). Patients with tumor progression during irinotecan treatment continued on the same dose and schedule of irinotecan with cetuximab , a response was noted in 27 of 121 (22.5%). patients, with a median duration of response of 186 days. The proposal that cetuximab may have anti-tumor activity as a single agent, may revert chemotherapy-resistance or a combination of both effects was unsure. Saltz and colleagues demonstrated partial responses of 10.5% of 57 patients and disease stability of 36.8% in those who failed irinotecan and subsequently treated with single agent cetuximab (100). Cunningham also demonstrated a favorable time to disease progression noted when cetuximab was used in combination, rather than as single agent therapy, even in patients recently demonstrating some chemotherapy resistance (101).

4.3.3. Potential Toxicities

Cetuximab is generally very well tolerated with allergic reactions, acne type skin rashes, abdominal pain, nausea, vomiting and asthenia being the most common grade 3/4 adverse events occurring in monotherapy. Skin rash has been reported with an incidence of >60% in the majority of trials, predominantly on the face and upper torso. It is usually not dose-limiting and resolves off treatment within 1-2 months. Anaphylactic reactions have been noted in 2% of patients.

5. CONCLUSIONS

Traditionally cancer therapy encompassed non-selective treatments, with the potential for significant toxicity to normal host tissues. Improved understanding of tumor biology has allowed the development of targeted therapy. Monoclonal antibodies are engineered to be highly

specific with limited toxicities however limitations remain. The role of monoclonal antibody therapy continues to expand, as clinical trials are performed in patients with early stage disease alone and in combination with other therapies, such as traditional cytotoxic chemotherapy, molecularly targeted therapy, other antibodies, vaccines, biologic agents, and radiation therapy.

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Send correspondence to: Michael R. Bishop, M.D., Experimental Transplantation and Immunology Branch, Center for Cancer Research/National Cancer Institute/National Institutes of Health, Building 10, Room 12N226, Bethesda, MD 20892, Tel: 301-35-2764, Fax: 301-480-4354, E-mail:mbishop@mail.nih.gov

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