

Adverse effects of the humanized antibodies used as cancer therapeutics

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Purpose of review

Humanized monoclonal antibodies represent a recent and very significant addition to the anticancer armamentarium. With improved therapeutic strategies due to these agents, however, there are also various, sometimes unexpected, side effects.

Recent findings

Most of the monoclonal antibodies used in oncology share a risk of infusion-related manifestations, including the possibility of anaphylaxis; these reactions usually appear early on during the first administration. Hematological toxicity is also frequent, especially if the antibodies are associated with chemotherapy; the resulting neutropenia – and with some agents lymphopenia – is associated with an increased risk of infection. Cardiac failure and pulmonary complications have been reported with some of these agents, especially in patients with prior cardiac or pulmonary comorbidities.

Summary

Although consideration of these side effects is important in terms of prevention and therapy, overall they are relatively uncommon, making therapy with monoclonal antibodies quite safe in comparison with other therapeutic modalities used in cancer patients.

Keywords

adverse effects, biologic therapies, Bexxar (tosituzumab), Campath (alemtuzumab), Erbitum (cetuximab), Herceptin (trastuzumab), Mabthera (rituximab), Mylotarg (gemtuzumab)

Introduction

Recent success in the development of monoclonal antibody-based anticancer drugs has largely benefited from the advancements made in recombinant technologies and cell culture production [1]. As these new medications enter the clinical scene, it is important to recognize their potential toxicity. The purpose of the present review is to discuss the adverse effects of the US Food and Drugs Administration (FDA)-approved monoclonal antibody-based therapeutic anticancer drugs (see Table 1), for which there is already substantial clinical experience.

Campath (alemtuzumab)

Campath (alemtuzumab; Genzyme, Cambridge, Massachusetts, USA) is primarily indicated in patients with chronic lymphatic leukemia (CLL) or lymphomas [2]. It has also been used in patients with nonmalignant diseases such as rheumatoid arthritis, solid organ transplants or multiple sclerosis. It is increasingly used as a conditioning agent for bone marrow transplantation.

Hematological toxicity, sometimes serious and in rare instances fatal, occurs as pancytopenia or bone marrow hypoplasia, neutropenia, thrombocytopenia or anemia; rare cases of autoimmune thrombocytopenia or hemolytic anemia have been reported. Higher doses are associated with higher risk of these complications. While pancytopenia or bone marrow hypoplasia is relatively rare (6%), grade 3 or 4 anemia, neutropenia and thrombocytopenia occur in more than 50% of treated patients. Very low CD4 and CD8 counts are observed early after initiation of alemtuzumab and take several months to return to baseline levels. As a result of these changes (neutropenia and lymphopenia) infectious complications are common (43%) during therapy with alemtuzumab; sepsis or pneumonia has been reported in 15% of patients, often caused by various opportunistic agents such as cytomegalovirus, *Candida* spp., *Aspergillus* spp. and mucorales. Reactivation of hepatitis B virus and cytomegalovirus is not uncommon and requires close monitoring and early therapeutic intervention [3,4].

Since these infections have mainly been reported in alemtuzumab-treated patients with CLL, it is difficult to separate the respective role of the drug and the disease in the genesis of these infections. Prophylaxis directed against *Pneumocystis carinii* and herpetic infections decreases but does not eliminate the occurrence of these infections.

Curr Opin Oncol 18:316–320. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Oncology 2006, 18:316–320

Abbreviation

CLL chronic lymphatic leukemia

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1040-8746

Table 1 US Food and Drugs Administration approved mAb-based cancer drugs

Generic drug name	Trade name	Type	Target
Alemtuzumab	Campath-H1	Humanized IgG1/K	CD52
Bevacizumab	Avastin	Humanized IgG1/K	VEGF
Cetuximab	Mylotarg	Humanized IgG4/K-toxin conjugate	CD33
Ibritumomab	Zevalin	Mouse IgG1/K-chelator conjugate	CD20
Rituximab	Rituxan	Chimeric IgG1/K	CD20
Tositumomab	Bexxar	Mouse IgG2a/lamda and ¹³¹ I-labeled IgG2a/lamda	CD20
Trastuzumab	Herceptin	Humanized IgG1/K	HER-2

Alemtuzumab can result in serious infusion-related 'flu-like' reactions and patients should be carefully monitored during administration, especially initially [2]. The most commonly reported infusion-related adverse events were rigors (86%), fever (85%), nausea (54%), vomiting (41%) and hypotension (32%).

Low-dose alemtuzumab still induces significant responses in patients with CLL but with milder hematologic and extra-hematologic side effects and a low rate of infections, even in the presence of long-lasting severe immunosuppression [5].

Avastin (bevacizumab)

Avastin (bevacizumab; Genentech and Roche, Basel, Switzerland) is used for the treatment of colo-rectal cancer (in addition to other chemotherapeutic agents such as 5-FU or irinotecan), renal carcinoma, non-small-cell lung cancer and other tumors, presently under investigation [6].

Perhaps the most intriguing side effect with bevacizumab is the relatively high incidence of local complications at the site of the tumor: gastrointestinal perforation (1.4–2%) and hemorrhage from non-small-cell carcinoma (epidermoid histology) (9%), especially if located close to the great vessels or necrotic; cutaneous hemorrhage also occurs in 4% of treated patients [7].

There is also an increased risk of cerebral or cardiac ischemic events, especially in patients older than 65 years – the overall incidence is 4.5% compared with 2% in control groups. Hypertension is also more frequent in bevacizumab-treated patients; it seems to be dose dependent but it is usually mild and rarely requires discontinuation of therapy (0.7%) [8*]. Among other complications, mild proteinuria occurs in 23% of patients, with no renal function impairment, especially in patients with hypertension.

Cardiac failure has been observed more frequently in bevacizumab-treated patients, especially in those who have received anthracyclines or chest irradiation in the past (3% versus 1%).

Slower wound healing has been reported with bevacizumab after major surgery (10–20%) and may be an indication for delayed adjuvant therapy with this agent after colorectal or any other major interventions [9].

Erbitum (cetuximab)

Erbitum (cetuximab; Merck, Darmstadt, Germany) is currently used in patients with colorectal carcinomas that express epidermal growth factor receptor (usually in combination with chemotherapy, namely irinotecan); other indications such as head and neck carcinomas are being actively explored at the present time [10].

Infusion-related complications occur in 5% of patients, usually during the first infusion, and can be severe in 50%; the most common manifestations are bronchospasm, urticaria, hypotension, fever, chills, nausea and vomiting, skin rash and dyspnea. Dyspnea can occur as a manifestation of hypersensitivity but also much later (weeks) after the initiation of therapy, especially in patients with low performance status or respiratory comorbidity; it may be difficult in such patients to separate the negative effects of cetuximab and the consequences of the underlying disease or comorbidities.

Cutaneous reactions (maculo-papular rash, seborrheic dermatitis-like eruptions and acneiform rashes) are frequent (> 10%) and are usually associated with a favorable clinical response to cetuximab [11*]. These complications, including paronychia and squamous blepharitis, are usually manageable with local therapies such as antibiotics and corticosteroids [12].

Mylotarg (gemtuzumab)

Mylotarg (gemtuzumab; Wyeth, Ayerst, Philadelphia, Pennsylvania, USA) is used as a monotherapy for CD33-positive acute myeloid leukemia. Severe myelosuppression occurs when gemtuzumab is used at recommended doses. Patients with high peripheral blast counts may be at greater risk of tumor lysis syndrome and, in such patients, leukoreduction with hydroxyurea or leukopheresis should be considered prior to the administration of gemtuzumab to reduce the peripheral white count.

Gemtuzumab administration can result in severe hypersensitivity, including anaphylaxis, with various infusion-

related events, including severe pulmonary manifestations (especially in combination with tumor-lysis syndrome).

Hepatotoxicity, including severe hepatic veno-occlusive disease, has been reported with gemtuzumab administration, even in the absence of previous liver disease or stem-cell transplants, which are two conditions that increase the risk of severe hepatotoxicity, which occasionally is fatal.

Zevalin (ibritumomab)

Zevalin (ibritumomab; Schering, Berlin, Germany) is used in patients with relapsed or refractory low-grade follicular transformed B-cell non-Hodgkin's lymphoma. It is normally used in combination with rituximab and a radioactive chemical such as Iridium-111 and Ittrium-90.

Serious infusion-related side effects have been reported with ibritumomab administration (swelling of lips, tongue or face, difficulty in breathing, hypotension) as well as lung problems (difficulty in breathing, shortness of breath, increased coughing) and heart manifestations (chest pain, irregular heart beats).

Unusual bleeding or bruising has also been reported. Since ibritumomab is made from human plasma, it may contain infectious agents (e.g. viruses) that can cause infection. Live vaccines should not be given during treatment with this agent.

Mabthera (rituximab)

Mabthera (rituximab; Roche, Reinach, Switzerland) is indicated for the treatment of various non-Hodgkin's lymphomas alone or in combination with chemotherapy (e.g. CVP, CHOP).

The most common side effects are allergic reactions that usually occur early on after the first infusion; they consist of urticaria, fever, chills, angio-neurotic edema and hypotension. These reactions occur in about 18% of patients but are rarely severe [13].

Myelosuppression due to rituximab alone is infrequent (2–4%) and reversible; it increases in frequency when rituximab is combined with chemotherapy, with the exception of higher rate of neutropenia [14]. Lymphocyte B depletion occurs in 70–80% of patients and may be responsible for an increased rate of infections with no specific organisms being involved. Reactivation of hepatitis B and nonspecific hepatitis has been reported in patients receiving rituximab [15].

Rare cases of cardiac toxicity (chest pain, arrhythmias) have been reported, especially in patients with cardiac comorbidities, which makes the relationship with rituximab therapy difficult to establish.

Bexxar (tosituzumab)

Bexxar (tosituzumab; Corixa corporation, Seattle, Washington, USA) and Iodine 131 are indicated for the treatment of patients with CD20 antigen-expressed refractory, low-grade, follicular or transformed non-Hodgkin's lymphomas and in patients with rituximab-refractory non-Hodgkin's lymphomas [16].

Adverse effects consist mainly of hypersensitivity reactions (fever, rigors, chills, sweating, nausea, dyspnea and bronchospasm), including anaphylaxis. They occur in about 29% of patients within 14 days of the dosimetric dose and can be managed by slowing or temporarily interrupting the infusion. The administration of the drug has been associated with the development of anti-mouse antibodies; patients who are positive may be at increased risk for serious allergic reactions.

The majority of patients (70%) who receive the Bexxar regimen experience severe (grade 3 or 4) cytopenia: thrombocytopenia (53%) and neutropenia (63%), which can be prolonged (several weeks). As a result, bacterial infections are common (45%) and hematological supportive care is often required (27%).

Hypothyroidism, based on laboratory tests rather than on clinical signs or symptoms, has been reported in 18% of patients after a median follow-up of 16 months but can occur much later [17].

Finally, cases of myelodysplastic syndrome, secondary leukemias, and additional malignancies have been reported at a median follow up of 29 months; however, the exact risk of developing secondary malignancies in these patients treated with the Bexxar regimen cannot be determined in the absence of controlled studies.

Herceptin (trastuzumab)

Herceptin (trastuzumab; Genentech, San Francisco, California, USA) is indicated in patients with breast cancer significantly expressing HER-2, either alone or in combination with various chemotherapeutic agents (e.g. paclitaxel, docetaxel, vinorelbine). Overall, the addition of trastuzumab to chemotherapy does not significantly increase the frequency of side effects [18].

Infusion-related events are common but rarely severe and they are no different from the hypersensitivity reactions described for the other drugs reviewed here. They are more common, however, during the first administration [19].

Cardiac toxicity, presenting as cardiac failure, is associated with trastuzumab therapy in about 10% of patients. The risk is particularly elevated in patients who have already been treated with anthracyclines or high-dose cyclophosphamide. The risk of cardiac failure requires a

Table 2 Summary of the most common side effects observed with humanized antibodies used in oncological therapy

	Alemtuzumab	Bevacizumab	Cetuximab	Gemtuzumab	Ibritumomab	Rituximab	Tosituzumab	Trastuzumab
Infusion-related reactions	+	—	+	+	+	+	+	+
Hematologic toxicity	+	—	+	+	+	+	—	—
Infections	+	—	—	—	+	+	+	—
Tumor-site perforation or hemorrhage	—	+	—	—	—	—	—	—
Hypertension or cardiac or cerebral thrombotic events	—	+	—	—	—	—	—	—
Cardiac failure or arrhythmias	—	+	—	—	—	—	—	—
Slow wound healing	—	+	—	—	—	—	—	—
Skin manifestations	—	—	+	—	—	—	—	—
Dyspnea or pneumonitis	—	—	+	+	+	—	—	+
Hepatic toxicity	—	—	—	+	—	+	—	—
Secondary malignancies	—	—	—	—	—	—	+	—

close cardiac work-up before therapy and a continuous follow-up, although this complication tends to occur early on during treatment.

Serious pulmonary complications (pulmonary infiltrates, acute respiratory distress syndrome, pneumonitis, pulmonary edema, pleural effusion) have been reported during or after the administration of trastuzumab. In many of these patients, there was advanced metastatic pulmonary disease or a serious pulmonary comorbidity; such conditions may be a contra-indication for the administration of trastuzumab.

More recently, pertuzumab, a recombinant humanized monoclonal antibody, which binds to the extracellular domain of the HER-2 receptor and blocks its ability to dimerize with other HER receptors, has been investigated in phase I studies [20]. Overall, it has been found to be well tolerated. The most common adverse effects were nonspecific (asthenia, nausea, aspecific skin rash, mild diarrhea, pain, anemia) and most were either grade 1 or grade 2 in severity. In these preliminary and limited studies, no significant cardiac, pulmonary or infusion-related toxicity was found.

Biologic therapies used for nononcological diseases

Tumor necrosis factor antagonists have set a new therapeutic standard for rheumatoid arthritis and other inflammatory diseases such as Crohn's disease, ulcerative colitis and multiple sclerosis. Infliximab, etanercept and adalimumab have demonstrated significant activity for rheumatoid diseases and Crohn's disease. The adverse effects have primarily been infection with *Mycobacterium tuberculosis*; however, other opportunistic infections such as histoplasmosis, *Pneumocystis carinii* infection, listeriosis and aspergillosis have also been reported.

Congestive heart failure has been suspected with the tumor necrosis factor antagonists but has not been

confirmed. The occurrence of secondary malignancies is an issue given the immunosuppressive nature of the antagonists. Current data suggest a higher rate of lymphomas in patients receiving the drugs [21].

Natalizumab, a selective adhesion-molecule blocker (monoclonal antibody against $\alpha 4$ integrins) has been used in patients with Crohn's disease and multiple sclerosis. Progressive multifocal leukoencephalopathy was occasionally reported after therapy with natalizumab for either disease [22,23*].

Other monoclonal antibodies for use in various diseases have been reviewed, however clinical experience is sometimes too limited to allow a clear picture of the potential side effects [24*]. Given the multiple actions of these new biological compounds, it is imperative to look for unusual toxicities beyond those already established (Table 2).

Conclusion

Although consideration of side effects is important in terms of prevention and therapy, overall they are relatively uncommon, making therapy with monoclonal antibodies quite safe in comparison with other therapeutic modalities used in cancer patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

- 1 Zhengxing Qu, Griffiths GL, Wegener WA, *et al.* Development of humanized antibodies as cancer therapeutics. *Methods* 2005; 36:84–95.
- 2 Tahar HA. Alemtuzumab for B-cell chronic lymphocytic leukaemia. *Issues Emerg Health Technol* 2005; 66:1–4.
- 3 Iannitto E, Minardi V, Calvaruso G, *et al.* Hepatitis B virus reactivation and alemtuzumab therapy. *Eur J Haematol* 2005; 74:254–258.
- 4 Robak T. Alemtuzumab in the treatment of chronic lymphocytic leukaemia. *BioDrugs* 2005; 19:9–22.
- 5 Laurenti L, Piccioni P, Tarnani M, *et al.* Low-dose intravenous alemtuzumab therapy in pretreated patients affected by chronic lymphocytic leukemia: a single center experience. *Haematologica* 2005; 90:1143–1145.

- 6 Motl S. Bevacizumab in combination chemotherapy for colorectal and other cancers. *Am J Health Syst Pharm* 2005; 62:1021–1032.
 - 7 Mulcahy MF, Benson AB III. Bevacizumab in the treatment of colorectal cancer. *Expert Opin Biol Ther* 2005; 5:997–1005.
 - 8 Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350:2335–2342.
- Interesting paper stressing the problem of gastrointestinal perforation.
- 9 Ellis AM, Curley SA, Grothey A. Surgical resection after downsizing of colorectal liver metastasis in the era of bevacizumab. *J Clin Oncol* 2005; 23:4853–4855.
 - 10 Burtneß B. Cetuximab and cisplatin for chemotherapy-refractory squamous cell cancer of the head and neck. *J Clin Oncol* 2005; 23:5440–5442.
 - 11 Thomas M. Cetuximab: adverse event profile and recommendations for toxicity management. *Clin J Oncol Nurs* 2005; 9:332–338.
- Comprehensive review for practical management.
- 12 Tonini G, Vincenzi B, Santini D, *et al.* Ocular toxicity related to cetuximab monotherapy in an advanced colorectal cancer patient. *J Nat Cancer Institute* 2005; 97:606–607.
 - 13 Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005; 7 (Suppl 3):S19–S25.
 - 14 Kimby E. Tolerability and safety of rituximab. *Cancer Treat Rev* 2005; 31: 456–473.
 - 15 Zell JA, Yoon EJ, Ignarus Ou SH, *et al.* Precore mutant hepatitis B reactivation after treatment with CHOP-rituximab. *Anticancer Drugs* 2005; 16:83–85.
 - 16 Horning SJ, Younes A, Jain V, *et al.* Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol* 2005; 23:712–719.
 - 17 Wahl RL. Tositumomab and (131) I therapy in non-Hodgkin's lymphoma. *J Nucl Med* 2005; 46:128S–140S.
 - 18 Marty M, Cogenitti F, Maraninchi D, *et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005; 23:4265–4274.
 - 19 Baselga J, Carbonell X, Castanedo-Soto NJ, *et al.* Phase II study of efficacy, safety and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol* 2005; 23:2162–2171.
 - 20 Agus DB, Gordon MS, Taylor C. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. *J Clin Oncol* 2005; 23:2534–2543.
 - 21 Keystone EC. Safety of biologic therapies: an update. *J Rheumatol* 2005; 32:8–12.
 - 22 Van Assche G, Van Ranst M, Sciort R, *et al.* Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; 253:362–368.
 - 23 Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005; 353:369–374.
- Not described for antibodies used in oncology, but more clinical experience is needed.
- 24 Siberil S, Dutertre CA, Box C, *et al.* Therapeutic monoclonal antibodies: a short historical perspective, a lot of engineering, and ... some clinical successes. *Transfusion Clin Biol* 2005; 12:114–122.
- Interesting review about the development of these antibodies, although pessimistic in terms of application.