JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article:
SHARMA R.Novel ANTICANCER MONOCLONAL ANTIBODIES.Journal of Clinical and Diagnostic Research [serial online] 2008 October [cited: 2008 October 6]; 2:1126-1132.
Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2008&month=October &volume=2&issue=5&page=1126-1132 &id=288

REVIEW ARTICLE

Novel Anticancer Monoclonal Antibodies

SHARMA R

ABSTRACT

The recent clinical success of anticancer antibodies like rituximab and trastuzumab has created great interest in antibody-based therapeutics for hematopoietic and solid tumor malignancies. The objective of this study is to review monoclonal antibodies (MAbs) used in oncology and to describe their pharmacological characteristics. Prominent general/internal medicine journals (MEDLINE, EMBASE, PUBMED between 2000 and 2007) were searched for review papers and clinical trials published on MAbs as novel anticancer drugs. These anticancer MAbs act by inducing lysis of cancer cells (rituximab, alemtuzumab), by targeting receptors involved in cell growth and proliferation of cells (trastuzumab, cetuximab, bevacizumab) and by delivering radioisotopes to cancer cells (tositumomab conjugated with I^{131}) and cytotoxic molecule (gemtuzumab). Therapy with MAbs has been recognized as a promising therapeutic tool in the field of oncology and a large number of molecules are currently undergoing clinical trials. It is hoped that rational development of combinations of multiple therapies directed at different targets, along with unique chemotherapy agents, MAbs and antisense or other cytokines will lead to more effective approaches for cancer patients.

Key Words: Rituximab, Alemtuzumab, Cetuximab, Tositumomab, Gemtuzumab.

Corresponding Author:
Dr. Rashmi Sharma
MD(Pharmacology), DMCH.
J&K Health Services Jammu-180004.
E.mail: rashmichams@yahoo.com

Novel Anticancer Monoclonal Antibodies

Cancer is a disease of cell characterized by a shift in the control mechanisms that govern cell proliferation and differentiation. There have been numerous advances in the pathogenesis of cancer; as a result, significant progress has been made and is still being made in the development of novel anticancer drugs. Drugs that have recently entered development are targeted to interfere with cell differentiation, metastasis, and angiogenesis. Hypoxic tumor stem cells specific agents, radio-sensitizing agents, normal tissue radio-protecting agents and biologic response modifiers are other drugs under development. Monoclonal antibodies (MAbs) targeting the receptors of growth factors or antigens on the cell surface are an important strategy for antitumor therapy. The introduction of MAbs into the treatment of cancer has led to remarkable improvements in patient survival. The recent clinical success of anticancer antibodies like rituximab and trastuzumab has created great interest in antibody-based

therapeutics for hematopoietic and solid tumor malignancies [1].

The objective of this study is to review MAbs used in oncology and to describe their pharmacological characteristics. Prominent general/internal medicine journals (MEDLINE, EMBASE, PUBMED between 2000 and 2007) were searched for review papers and clinical trials published on MAbs as novel anticancer drugs. All the data was collected and novel MAbs in use and under development as important anticancer therapies are summarized in the present article.

Strategies For The Employment Of Mabs

Immune reaction directed destruction of cancer cell, interference with the growth and differentiation of malignant cells, antigen epitope directed transport of anti-cancer agents to malignant cells, anti-idiotype vaccines, and development of engineered (humanized) mouse monoclonals for anti-cancer therapy are some of the strategies for the employment of antibodies for anti-cancer therapy[2]. Moreover, a variety of different agents (e.g., toxins, radionuclides, chemotherapeutic drugs, etc.) have been conjugated to mouse and human MAbs for selective delivery to cancer cells[3].

Types Of Mabs[4]

MAbs can be obtained from [a] murine hybridomas produced by fusion of B-lymphocytes from immunized mice or rats with murine myeloma cells (Murine MAbs) or [b] these are the combinations of the antigen-binding parts of the mouse antibody with the effector parts of a human antibody (Chimeric MAbs), e.g. infliximab, rituximab and abciximab or [c] they can be Humanized MAbs, which bind with the amino acids forming the antigen binding site of a mouse/ rat antibody part of the human antibody molecule, thus replacing its own hypervariable regions , e.g. gemtuzumab ozogamicin, trastuzumab etc. The human MAbs are less immunogenic. Engineered MAbs have the advantages of decreased immunogenicity, enhanced half-life and optimized specificity.

Mabs Used In Anticancer Therapies

[Table/Fig 1] [Table/Fig 2]

(Table/Fig 1) Mechanism of action of various anti-cancer Monoclonal Antibodies.

Monoclonal Antibodies	Mode of action in cancer
Rituximab, Alemtuzumab	Induce lysis of cancer cells by altering host-immune response
Trastuzumab, Cetuximab, Bevacizumab	Bind with extracellular domains of the receptors involved in cell growth and proliferation
Tositumomab (conjugated with I^{131}, Ibritumomab [conjugated with Y^{90} and In ^{111}]	Deliver radioisotopes to cancer cells
Gemtuzumab, Calicheamicin	Deliver cytotoxic molecule

(Table/Fig 2) Various Anti-cancer Monoclonal Antibodies and their potential uses.

Anti-cancer Monoclonal Antibodies	Therapeutic uses
Trastuzumab	Relapsed breast cancer patients who express the HER2/neu protein product
Pertuzumab	Advanced breast cancer patients
Alemtuzumab	Fludarabine refractory Chronic Lymphocytic Lymphoma
Rituximab	b-cell malignancies, including follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, Waldenstrom's macroglobulinemia, mantle cell lymphoma, diffuse large-cell lymphoma and post-transplant lymphoproliferative disorders
Epratuzumab	Non Hodgkin's Lymphoma
Apolizumab	Lymphoid malignancies
Cetuximab	Epidermal growth factor receptor expressing, metastatic colorectal cancer in patients, who failed to improve with irinotecan-based chemotherapy or intolerant to irinotecan-based chemotherapy
Panitumumab	Renal, colorectal and non-small cell lung cancers
Bevacizumab	Metastatic colorectal cancer in combination with fluorouracil-based chemotherapy, breast, non-small-cell lung, pancreatic, prostate, renal and hepatic cancers, as well as for melanoma and acute myelogenous leukemia
Gemtuzumab ozogamicin.	CD33+ AML(acute myeloid leukemia) in first relapse and who are not considered candidates for cytotoxic chemotherapy, in combination with all-trans retinoic acid in the treatment of acute promyelocytic leukemia
Radiolabeled antibodies such as yttrium 90-ibritumomab tiuxetian (Y^{90}), indium 111-ibritumomab (In^{111}) and iodine 131-tositumomab (I^{131}sub)	Non Hodgkin's Lymphomas
MAb B43.13	Late-stage ovarian cancer with tumor- specific antigen CA-125
Mitumumab	Small Cell Lung Carcinoma, Melanoma and soft tissue sarcoma (CD11a)

Trastuzumab (Herceptin)[4],[5],[6]

It (humanized mab) is the first novel targeted therapy approved for routine clinical

application in advanced breast cancer, with HER2/ neu protein over expression, either as single agent or in combination with chemotherapy. It is an active agent in conjunction with paclitaxel chemotherapy in relapsed breast cancer patients who express the HER2/neu protein product. Phase I and II trials conducted by the gynecological oncology group demonstrated a response rate of ~10% in patients with ovarian cancer receiving anti-HER2/neu MAb. However, the drug is under-going testing in combination with platinum- and taxane-based chemotherapy to determine its activity in ovarian cancers. New combinations with endocrine therapy are currently being evaluated. Trastuzumab is generally well tolerated. So far, considerable cardiotoxicity was seen only in combination with doxorubicin. Thus, extensive cardio-monitoring is now performed in trials assessing further chemotherapeutic partners.

Pertuzumab[4]

It is another therapeutic MAb under clinical evaluation. It binds to a different epitope on HER2/neu than trastuzumab and inhibits heterodimerization with other HER receptors. Phase I data in patients with advanced breast cancer has shown that it is well tolerated and is clinically active, suggesting that inhibition of dimerisation may be an effective anticancer strategy.

Alemtuzumab (Campath-1H)

It is a humanized antiCD52 MAb approved by US FDA in May 2001 for treatment of fludarabine refractory CLL (Chronic lymphocytic leukemia)[5],[7].CD52 is expressed in virtually all lymphocytes at various stages of differentiation as well as in monocytes ,macrophages, eosinophils and tissues of the male reproductive system[5],[7]. The highest level is expressed on T-prolymphocytic leukemia (PLL), B-cell CLL. However, haematopoietic stem cells , erythrocytes and platelets do not express this antigen and are thus spared from a direct antibody effect .The antibody remains on the surface of target cells and acts possibly by antibody- dependent cellular toxicity, complement dependent cyto-toxicity and induction of apoptosis[5],[7]. However, infusion reaction, immuno-suppression and opportunistic infections present a challenge that may be overcome with altered schedules and routes of administration. Alemtuzumab has been evaluated in 50 patients with previously treated indolent lymphoma. In combination with rituximab it has produced a response in 10 out of 22 patients with CLL[8].Alemtuzumab has ability to achieve clinical remissions and to successfully purge minimal residual disease (MRD) from both blood and bone marrow in B-CLL patients[9].In a clinical trial, forty-one consecutive CLL patients underwent allogeneic hematopoietic cell transplantation after conditioning with fludarabine, melphalan and alemtuzumab[4].The alemtuzumab-based regimen showed a relatively low rate of graft versus host disease. However, transplant related mortality remains relatively high as a result of a variety of viral and fungal infections. Further, studies are on to test the efficacy of reduced doses of alemtuzumab in immunosuppressedpatients[10].

Rituximab (C2B8,Rituxan ,MabThera)

[7],[11],[12],[13],[14] It is a chimeric MAb against CD20 antigen present on B-cells , was approved in 1997 for treatment of relapsed or refractory low grade or follicular $CD20^{+}$ B cell indolent non Hodgkin's lymphoma (NHL) . The possible mechanism of action includes antibody- dependent cellular toxicity, complement mediated toxicity and induction of apoptosis; as well as the effects on B–cell activation and proliferation. Because of its activity, lack of cross resistance and minimal side effects ,it has now become the commonly employed therapy for B- cell malignancies ,complications of CLL or its therapy including

pure red cell aplasia and fludarabine–induced immune thrombocytopenia . However, it has limited activity as a single agent in patients relapsed or refractory after prior chemotherapy. Higher response rates are seen in previously untreated patients and when combined with chemotherapy drugs. Rituximab plus IL-2 (interleukin-2) has shown activity in a small series of patients with CLL. It has proven efficacy against a wide range of b-cell malignancies, including follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, Waldenstrom's macroglobulinemia, mantle cell lymphoma, diffuse large-cell lymphoma and post-transplant lymphoproliferative disorders. In indolent lymphoma that has progressed after prior chemotherapy, rituximab as a single agent is associated with 50-60% response rates in the relapsed setting and 60%- 75% as front-line therapy. However, it has greatest synergy or additive effects with the anthracycline, doxorubicin. It has been added as part of sequential therapy after chemotherapy, or as a consolidation treatment in patients who have already responded to chemotherapy. Rituximab was also used with biological-response modifiers in patients with relapsed low-grade lymphoma.

Epratuzumab (hLL2, E-mab; LymphoCide, Immunomedics, Inc, Morris Plains, NJ or AMG412, Amgen ,Thousand Oaks ,CA)

[15]CD22 is a 135-kd –cell-restricted sialoglycoprotien expressed in 60%-80% of B-cell malignancies and appears to play an important role in both B-cell adhesion and activation. Moreover, being a specific marker for most neoplastic and non neoplastic Bcells. It is a promising agent for the treatment .In vitro, MAb against CD22 induced cell death in several burkitts lymphoma cell lines and mediated antitumor effects in animal models. Epratuzumab, a humanised antiCD22 MAb developed to reduce the potential for immunogenicity, prolong half life and increase effector potential ,has been reported in a phase I/II trials to induce response in NHL. Ongoing and future studies will continue to define its therapeutic role due to the potential to improve effectiveness in combination with chemotherapy as compared to the standard regimens.

Anti-Cd23(Idec-152,Idec Pharmaceuticals)[7]

Since CD23 expression is a characteristic feature of CLL cells ,there is a role of anti-CD23 antibody ,which is a primatized MAb ,made from a primate source with strong similarity to the human antibody . It inhibits IgE secretion in vitro and induces apoptosis of lymphoma cell lines. Clinical trials of this antibody as monotherapy or in combination with rituximab are on going .

Apolizumab (Hu1D10)[7]

It is a MAb directed against a polymorphic determinant of HLA-DR and is present on both normal and on malignant cells from about half of the patients with lymphoid malignancies. It has been evaluated clinically and activity has been noted in phase-1 trial. The combination of Hu1D10 and rituximab is being evaluated at the National Cancer Institute .However toxicities in the form of infusional and allergic reactions as well as uremic syndrome are a matter of concern .

Cetuximab[4],[16]

It is a recombinant human/mouse chimeric epidermal growth factor receptor (EGFR) MAb. It is approved by the US FDA in February 2004 to be used in combination with irinotecan for EGFR-expressing, metastatic colorectal cancer in patients, who failed to improve with irinotecan-based chemotherapy or intolerant to irinotecan-based chemotherapy. In a Phase III trial, cetuximab was administered to 329 patients (irinotecan or oxaliplatin refractory). Partial response was achieved in 10.8% of patients who received cetuximab monotherapy and 22.9% of patients who received cetuximab plus irinotecan therapy (P = 0.007). The overall

response rate in two Phase II trials in EGFR-expressing, metastatic colorectal cancer refractory to irinotecan therapy with cetuximab ranged from 9% to 12%. The drug was well tolerated with proper administration precautions. Cetuximab is being evaluated in combination with radiation therapy and/or platinum in patients with squamous-cell head and neck cancer, as well as cetuximab in combination with various antineoplastic agents for non-small cell lung cancer and pancreatic cancer.

Panitumumab[4],[17]

It is the first fully human MAb that binds to EGFR. Phase III study results indicate a 46% reduction in the rate of tumor progression in patients with EGFR-positive metastatic colorectal cancer who have failed prior therapy compared with those who received best supportive care alone. It is well tolerated. However, acneiform rash is the most common dose-dependent adverse effect. Studies so far indicated a low rate of infusion-related reactions (1%, grade 3-4) with it. As it targets EGFR, which is over-expressed in lung, breast, bladder, pancreatic, colorectal, kidney and head and neck cancers, hence, it is being evaluated in renal, colorectal and non-small cell lung cancers.

Bevacizumab (Avastin)[4],[7],[18]

There is a potential role for angiogenesis in CLL since angiogenesis factors such as basic fibroblast growth factor upregulates Bcl-2 and results into delay in programmed cell death. Bevacizumab, an antivascular endothelial growth factor (antiVEnGF) Mab ,is currently being evaluated in solid tumors as well as lymphomas and may be of interest in CLL. Bevacizumab is a recombinant human MAb that inhibits the biological activities of VEnGF. It has both cytostatic and cytotoxic effects, resulting in a reduction in tumor growth and increase in median survival time and time to tumor progression. It is approved as an intravenous agent for use in the first-line treatment of metastatic colorectal cancer in combination with fluorouracil-based chemotherapy. Bevacizumab has also yielded preliminary evidence of efficacy for breast, non-small-cell lung, pancreatic, prostate, renal and hepatic cancers, as well as for melanoma and acute myelogenous leukemia.

Gemtuzumab Ozogamicin[4],[19]

It is a humanized MAb directed against CD33 linked to a calicheamicin derivative. It is a member of the enediyne family of antitumor antibiotics. It gets rapidly internalized after binding to its target, followed by the release of the potent antitumor calicheamicin derivative. It induces breaking of double-stranded DNA, resulting in apoptosis. It is approved for the treatment of elderly patients ($\geq$ 60 years) with CD33+ AML (acute myeloid leukemia) in first relapse and who are not considered candidates for cytotoxic chemotherapy. It has been used in combination with all-trans retinoic acid in the treatment of acute promyelocytic leukemia with favorable response.

Radiolabeled Anti-CD20 Antibodies

[3],[4],[20],[21] Radiolabeled antibodies such as yttrium 90-ibritumomab tiuxetian (Y^{90}), indium 111-ibritumomab (In^{111}) and iodine 131-tositumomab (I^{131}sub) are seem to be even more efficacious than MAbs in the treatment of non Hodgkin's Lymphomas. In relapsed indolent lymphoma, response rates of up to 80% have been noted with ibritumomab tiuxetian (Y90), compared to 56% with rituximab.

Tositumomab and iIodine (I^{131}) tositumomab is administered in two steps. The dosimetric step determines individual patient pharmacokinetics, allowing a patient- specific dose to be calculated. This is followed by the therapeutic step, with administration of the therapeutic dose between 7 and 14 days after the dosimetric dose. HMFG1 is a murine immunoglobulin G1 monoclonal antibody developed at the Imperial Cancer Research Fund (London UK) with specificity to an epitope of polymorphic epithelial mucin, which is expressed by more

than 90% of epithelial ovarian cancers and many other carcinomas. In phase I and Phase II studies antibody directed to HMFG1 (labeled with ^{90}Y) was found to be well tolerated and efficient to prolong the survival in patients with microscopic residual disease after induction chemotherapy.

Anti-CA125 Mab[5]

MAb B43.13 is a murine MAb to the tumor-specific antigen CA-125, which is found in more than 90% of patients with late-stage ovarian cancer. MAb B43.13 binds to the circulating CA125 antigen with high affinity to form complexes that the body recognizes as foreign because the complex includes the foreign antibody. These immune-complexes result into induction of CA-125 specific antibodies, T-helper cells and cytotoxic T-cells. Administered via 20 minute intravenous infusion, low dose MAb B43.13 is well tolerated than murine MAb. The possible therapeutic value of the low dose MAb approach was serendipitously discovered in a diagnostic study with MAb B43.13, which was used as tumor-imaging agent for nuclear medicine because of its high affinity for the ovarian cancer marker CA125.In a study where technetium-99m-radiolabeled MAb B43.13 was used for the immunoscintigraphic detection of recurrent ovarian cancer, it was found that a large number of patients showed unexpectedly long survival time. Recently the utility of MAb B43.13 is being explored in various clinical applications combined with standard treatments of ovarian cancers. The data collected till date regarding effects of MAb B43.13 administered for recurrent ovarian cancer or during watchful waiting stage after surgery or chemotherapy indicate that MAb B43.13 prolongs survival and increases the time to relapse in selected patients with ovarian cancer. However, the use of MAb B43.13 has not yet been studied in conjunction with the first line therapy. Traditional thinking has discouraged this approach because the immuno-suppressive properties of first line therapy may abalate the immuno-stimulatory effects of the antibody treatment. However, the phase II data generated with MAb B43.13 in patients with recurrent disease and concurrent chemotherapy indicate that study of first line therapy could be considered. Moreover, concomitant use of chemotherapeutic agents along with MAb B43.13 resulted into induction of cytotoxic T-cells without affecting safety profile of either MAb B43.13 or chemotherapeutic agents. CA125, the ovarian cancer marker to which MAb B43.13 binds, is also found in the patients with other cancer types. Hence, MAb B43.13 has potential role in various other cancer types.

Mitumumab[4]

Mitumumab is indicated in the treatment of SCLC(small cell lung carcinoma), Melanoma and soft tissue sarcoma (CD11a).

Immunotoxins[7]

These are comprised of peptides, usually an antibody or growth factor ,linked to a toxin such as diphtheria toxin ,pseudomonas exotoxin or ricin .Anti-B4 (CD19)-blocked ricin is a halotoxin from which the binding domain has been removed and a tumor specific ligand is added .Binding to normal cells is then chemically blocked .BL22 is immunotoxin directed against CD22 and fused to truncated pseudomonas exotoxin that has been proved successful in treatment of nucleoside analog refractory hairy cell leukemia .This novel agent is being explored as a potential treatment for CLL. Fusion protein Denileukin diftitox (Ontak,Seragen, Inc, San Diego, CA) ,a diphtheria–IL-2 immunotoxin approved for the treatment of cutaneous T-cell lymphomas , is directed at a specific target IL-2 (interleukin –2) receptors on the surface of malignant cells and is in phase II clinical trials in CLL. Its side effects include infusion related events, a vascular leak syndrome and elevation of hepatic enzymes.

A combination of various novel approaches to anticancer treatment has more potential values than a single agent. However, an ideal anticancer drug should eradicate cancer cells without harming normal tissue. Till date currently available agents do not meet this

criterion. Therapy with MAbs has been recognized as a promising therapeutic tool in the field of oncology and a large number of molecules are currently undergoing clinical trials. It is hoped that rational development of combinations of multiple therapies directed at different targets, along with unique chemotherapy agents, MAbs and antisense or other cytokines will lead to more effective approaches for cancer patients .

References

[1]. Ross JS, Gray K, Gray GS, Worland PJ, Rolfe M. Anticancer antibodies. Am J Clin Pathol 2003 ;119(4):472-85.

[2]. Kaur J, Badyal DK, Khosla PP. Monoclonal antibodies:Pharmacologicalrelevance.Indi anJ Pharmacol 2007;39:5-14.

[3]. Bodey B, Bodey B, Siegel SE, Kaiser HE. Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents. Curr Pharm Des 2000;6: 261-76.

[4]. Gupta N, Srivastava A. Monoclonal antibodies: Targeted therapy. Indian J Pharmacol 2006;38:390-6.

[5]. Berek JS, Schultes BC and Nicodemus CF. Biologic and Immunologic Therapies For Ovarian Cancer. J Clin Oncol 2003; 21:168s-74.

[6]. Dillman RO. Perceptions of Herceptin: A monoclonal antibody for treatment of breast cancer. Cancer Biother Radiopharm 1999;14:5-10.

[7]. Mavromatis Band Cheson BD . Monoclonal antibody therapy of chronic lymphocytic leukemia. J Clin Oncol 2003;21(9) :1874-81.

[8]. Faderl S, Thomas DA, O'Brien S. An exploratory study of the combination of monoclonal antibodies Campath- IH and rituximab in the treatment of CD-52 and CD20 positive chronic lymphoid disorders. Blood 2001;98:365.

[9]. Montillo M, Schinkoethe T, Etler T. Eradication of minimal residual disease with alemtuzumab in B-CLL patients:The need for a standard method of detection and the potential impact of bone marrow clearance on disease outcome. Cancer Invest 2005;23:488-96.

[10]. Delgado J, Thomson K, Russell N, Ewing J, Stewart W, Cook G, et al . Results of alemtuzumab - based reduced intensity allogenic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. Blood 2006;107:1724-30

[11]. Hainsworth JD, Litchy S, Barton JH, Houston GA, Hermann RC, Bradof JE et al. Single agent rituximab as first line and maintenance treatment for patients with chronic lymphocytic leukemia: A phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2003; 21(9): 1746-51.

[12]. Kosmos C, Stamatopoulos K, Stavroyianni N, Savaris N and Papadaki T. Anti-CD20- based therapy of B cell lymphoma: state of the art. Leukemia 2002;16: 2004-5.

[13]. Grillo-Lopez AJ, Hedrick E, Rashford M, Benyunes M. Rituximab: Ongoing and future clinical development. Semin Oncol 2002;29:105-12.

[14]. Montserrat E. Rituximab in chronic lymphocytic leukemia. Semin Oncol 2003;30: 34-9.

[15]. Leonard JP, Coleman M, Ketas JC, Chadburn A,Ely S , Furmann RR et al . Phase 1/11 trial of epratuzumab (Humanized anti –CD22 antibody) in indolent non hodgkins lymphoma . J Clin Oncol 2003;21 :3051-9 .

[16]. Wong SF. Cetuximab: An epidermal growth factor receptor monoclonal antibody for the treatment of colorectal cancer. Clin Ther 2005;27:684-94.

[17]. Saadeh CE, Lee HS. Panitumumab: a fully human monoclonal antibody with activity in metastatic colorectal cancer. Ann Pharmacother 2007;41(4):606-13.

[18]. Motl S. Bevacizumab in combination chemotherapy for colorectal and other cancers. A J Health Sys Pharm 2005;62:1021-32.

[19]. Estey EH, Giles FJ, Beran M, O'Brien S, Pierce S A, Stefan H, et al . Experience with gemtuzumab ozogamicin and all-trans retinoic acid in untreated acute promyelocytic leukemia. Blood 2002;99:4222-4.

[20]. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmaanouilides C, Joyce R, et al Randomized controlled trial of yttrium 90 labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low grade, follicular or transformed B-cell non-Hodgkins lymphoma. J Clin Oncol 2002;20:2453-63.

[21]. Davies AJ. A review of tositumomab and I131 tositumomab radioimmunotherapy for the treatment of follicular lymphoma. Expert Opin Biol Ther 2005;5:577-88.