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Clinical Applications of Targeted Therapeutics

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1. INTRODUCTION

The acceptance of monoclonal antibody (MAb)-based therapies in the treatment of human cancer has been slow but many of the obstacles identified by the initial trials have now been overcome and objective tumor regression has been obtained in lymphomas, several types of leukemias, breast cancer, colon cancer, and melanomas (1–3). The tumor-associated antigens (TAAs) or other molecules that have been targeted by MAbs for the treatment of human cancer have been listed by Scott and Welt (2). Most impressive results have been obtained using MAbs against the idiotype of B cells, CD20 on malignant B cells, CD33 on leukemic blast cells, and Her2/neu on breast-cancer cells.

2. LYMPHOMAS, LEUKEMIAS, AND PLASMA-CELL MALIGNANCIES

Hematological malignancies constitute about 9% of all malignancies in the USA (4). Malignant lymphomas are one of the 10 most frequent cancers worldwide with about a 7% increase in their prevalence per year (5). Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphomas that arises from the lymphocytes in spleen, thymus, and lymph nodes. NHLs are the most common hematopoietic neoplasms account-

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ing for approx 4% of all cancer diagnoses. Approximately 75% of NHLs arise from B cells, 20% from T cells, 4% from null cells, and 1% from histiocytes (6). Low-grade and follicular lymphomas are the most common B-cell malignancies in the Western hemisphere. They usually have an indolent course. Even though there has been impressive progress in the clinical management of hematological malignancies, cure rate is still dismal (7). For example, in high-grade NHLs, in spite of the high rate of initial response to combination chemotherapy, 50–70% of patients relapse and die of the disease. In patients with low-grade B-cell NHL, only a small proportion of patients with limited disease can be saved. Thus, there is a need to develop innovative methods of treatment for improving the survival and the quality of life of these patients. The use of MAbs is one of the several new approaches that are now being used in the clinic to further improve the results of treatment of cancers of the hemopoetic system.

2.1. Non-Hodgkin's B-Cell Lymphomas (B-Cell NHL)

2.1.1. UNCONJUGATED MAbs

2.1.1.1. Anti-Id Antibodies. The first successful use of a MAb in the treatment of cancer was by Miller et al. when they treated a B-cell lymphoma patient with an anti-Id MAb (8). The results of the treatment of 52 B-cell NHL patients with anti-id MAbs have been summarized by Levy (9). A majority of patients had significant tumor regression including complete regression lasting 10 years or longer. Adding interferon alpha (IFN- α) (10) or chlorambucil (11) to anti-id antibodies did neither add to the antitumor effect of antibodies alone nor did they affect the emergence of clones that did not react with the therapeutic antibody. The clinical use of anti-id MAbs have several limitations, i.e., difficulty in the production of patient-specific MAbs; the neutralization of anti-Id antibodies by circulating Id-containing products of the neoplastic clones, and the selection of malignant B-cell clones that express Id-variants that do not bind the MAb. To overcome the problem of Id-variants, attempts have been made to target different epitopes of the idiotype with a second or third anti-Id MAb (10). To avoid the problems associated with the production of patient-specific anti-Id MAbs, TAAs, which are expressed by more than one patient's tumor cells, are now favored for therapeutic targeting. These more generic NHL B cell-associated TAAs include the lineage-specific antigens CD20, CD19, CD10, CD5, or Lym1. Anti-CD20 MAbs have produced the most encouraging results in the treatment of B-cell lymphomas. The chimeric anti-CD20 MAb, IDEC-C2B8 (Rituximab), is currently the MAb of choice for the treatment of non-Hodgkin's B-cell lymphomas.

The CD20 antigen is a 297-amino acid phosphoprotein expressed only by cells of B-lymphocyte lineage but not by pro-B cells and minimally by plasma cells. It is expressed on normal mature B cells and in high density ($>100,000$ mol/cell) on all malignant B cells in more than 90% of B-cell lymphomas such as follicular, mantle-cell, and prolymphocytic lymphomas; also in some large-cell NHLs and hairy-cell leukemias (12–14). CD20 is also expressed in lower density on malignant B cells of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (12). The function and the natural ligand of CD20 are not known. CD20 is neither secreted nor is it shed or substantially internalized after binding to anti-CD20 MAbs (15). Rituximab is a high-affinity humanized anti-CD20 MAb. In initial trials, rituximab was used as a single agent in low-grade NHL. More recent trials have included patients with aggressive NHLs, mantle-cell lymphoma, post-transplantation lymphomas, and

other types of NHLs in previously untreated as well as relapsed patients. Results have been presented and reviewed by a number of authors (9,12,16,17–26). Best results were obtained in follicular lymphoma patients with low tumor burden (18,19). Response rate varied from 54–73%. In one study (20), 10/49 patients had complete molecularly confirmed remission. In patients with refractory (21) or bulky disease (22), overall response rates were 57% (14% complete response [CR]; 43% partial response [PR]) in refractory disease and 43% in bulky disease. Single-agent rituximab had moderate effect in mantle-cell lymphoma and immunocytoma but was much less effective in small lymphocytic lymphoma (23,24). Rituximab induced complete remission in 2/3 patients with post-transplant lymphoproliferative disease (25) and 3/3 patients with post-transplant Epstein-Barr virus (EBV) lymphoma (26). Combining rituxan with the standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen in the treatment of aggressive B-cell lymphomas, neither added to the toxicity of CHOP nor improved the results of CHOP therapy alone (27). Adding IFN- α to rituximab induced 8% CR and 50% PR in a group of 26 follicular lymphoma patients (28). In a group of seven intermediate-grade NHL patients who had progressive disease after chemotherapy and peripheral stem-cell transplantation, rituximab induced 2 CR and 1 PR at the 204th median day of follow-up (29). Comparison between different treatment groups is difficult because the trial groups are small and the criteria for inclusion in these trials were different. The follow-up periods in these studies are relatively short but still it appears that the remissions induced by anti-CD20 MAbs are temporary. In one study (19) regressions had a median duration of ~13 mo but subsequent remissions tended to last longer.

2.1.1.2. Anti-CD52 MAbs (CAMPATH-1 MAbs). CD52 is a nonmodulating, 21 kD–28kD antigen consisting of a 12 amino acid residue linked to the cell membrane by a glycosylphosphatidylinositol anchor. Approximately 500,000 copies of CD52 are expressed on mature T and B lymphocytes and monocytes but not on their stem cells. Anti-CD52 MAbs lyse CD52-expressing cells by both ADCC and C'-mediated pathways (30,31). A Phase I/II trial of CAMPATH-1H was abandoned because of toxicity and lack of efficacy of the MAb (32).

Finally, the Id-containing monoclonal products B-cell lymphomas and leukemias have been used as tumor-specific vaccines to induce antitumor immune response. About 50% of the vaccinated patients produced anti-Id antibody. The responders had significant prolongation of remission and survival (9,33).

2.1.2. RADIOIMMUNOTHERAPY (RIT) OF B-CELL NHL

Although the results obtained with unconjugated rituximab in the treatment of B-cell NHL have been very promising, limitations of unconjugated MAbs are now quite obvious. For example, 40–50% low-grade lymphomas and 60–70% aggressive lymphomas do not respond to rituximab and only 5–10% remissions are complete and lasting. RIT is one method for increasing the potency of rituximab and other B-cell antibodies because it adds another mechanism of tumor cell kill to the cytotoxic mechanisms of unconjugated MAbs. Furthermore most hematological malignancies are very radiosensitive and the “cross fire” effect of beta particles emitted by the radioisotopes used for RIT can eliminate nearby antigen-negative malignant cells.

The antigens targeted for the RIT of B-cell NHLs include CD19, CD20, CD22 (34,35), CD37 (36,37), Id-IG (38), and a MHC class II allele HLA-DR 10 cell surface antigen (39). CD 20 is now the target antigen of choice.

The radionuclides that have been used in the RIT of B-cell NHLs are ^{131}I , ^{90}Y (with ^{111}In for immunoscintigraphic evaluation) (38,40,41) and ^{67}Cu (42). Because of its availability, low cost, and ease of conjugation chemistry, ^{131}I has been used more often than ^{90}Y despite the latter's more energetic (and therefore therapeutically more effective) beta emissions and a more suitable physical $t_{1/2}$.

Results of RIT of B-cell lymphomas have been recently summarized by Press (43), DeNardo et al. (44), Buske et al. (16), Wilder et al. (45), and Davis and Knox (46). In brief, two strategies have been adopted in the RIT of B-cell NHLs. In the first strategy, myeloablative doses are delivered along with peripheral-blood stem-cell transplantation (43,47). However the second or lower nonmyeloablative fractionated treatment strategy (48) has produced almost equally good results. Highest response rates (including complete response) and longest remissions have been obtained with anti-CD20 MAbs. As stated, unconjugated anti-CD20 MAbs induced 60% remissions (including 5–10% CR) in relapsed follicular lymphoma, but ^{131}I or ^{90}Y labeled anti-CD20 MAbs induced 71–80% remissions (including 34–40% CR) at nonmyeloablative doses and 85–90% remissions (including 75–80% CR) at myeloablative dose regime (43). There were significantly more responders in patients with low-grade or transformed NHL than in patients with *de novo* intermediate-grade NHL (48). The median progression-free survival was 12 mo for all responders and 20.3 mo for those with PR (48). Reversible myelotoxicity has been the main toxicity especially at higher doses. Non-hematological toxicities include thyroid dysfunction and usually mild (Grade 1) chill, fever, nausea, muscle pain, etc., which are mostly related to the carrier MAb.

2.1.2.1. Combination of RIT and Chemotherapy in B-Cell NHL. To further improve the response rates and durations of response achieved by RIT in the treatment of NHL, Press and his colleagues demonstrated that in vitro there was marked synergism between ^{131}I -labeled anti-CD20 MAb and the nucleoside analogues cytarabine or flutabine; moderate synergism with a camptothecin analogue, etoposide, or doxorubicin; and no synergism with a cyclophosphamide metabolite, cisplatin, or 5FU (49). A Phase I/II trial with myeloablative doses of ^{131}I linked anti-CD20 MAb, followed by the administration of etoposide and cyclophosphamide and then autologous stem-cell transplantation indicated some improvement in overall survival and progression-free survival (50).

2.1.3. IMMUNOTOXIN (IT) THERAPY OF B-CELL NHL

The recent results of IT therapy of B-cell lymphomas have been summarized by Buske (16), Kreitman (51), Grossbard et al (52). The toxin components in most of the ITs used in clinical trials have been deglycosylated ricin A chain or ricin A chain with blocked galactose-binding sites. The antigens that have been most often targeted are CD19 (52,53), CD22 (53), and interleukin (IL)-2R (or CD25). CD 25 has been targeted by anti-CD25 (or anti-Tac) MAbs (54) or its natural ligand, IL-2 (55). CD22 targeting has yielded highest response rates including long-lasting, complete remissions (56,57). This may be due to better internalization and intracellular processing of ITs (51).

These clinical trials have demonstrated potent antitumor activity of ITs, but the therapeutic efficacy of ITs has been severely limited by their unacceptable toxicity, high immunogenicity (of both antibody and toxin moieties), rapid clearance from the circulation, and poor penetration into tumor masses. To avoid the problems of immunogenicity and penetration into solid tumors, ITs have been administered as continuous

infusions at frequent intervals to NHL patients in complete remission (52). Twenty-six of 31 patients given an anti-CD 19-bR IT remained in CR after a median follow up of 54.5 mo. However 4-yr follow-up data showed increasing relapse. Toxicity was reversible. Twenty-three of 31 patients had developed antibody against one or both components of the IT.

Combination therapy with dgA-linked anti-CD19 and anti-CD22 MAbs (Combotox) had unpredictable clinical results, including two deaths probably related to the ITs (53). IT therapy in patients with prior extensive radiotherapy also had unacceptable side effects (58).

2.1.4. BISPECIFIC ANTIBODIES IN B-CELL NHL

Recently CD3 \times CD19 bispecific MAb constructs have been used, with (59) and without (60) co-administration of anti-CD28 MAb for costimulation, to eliminate residual tumor cells after cytotoxic therapy of NHL. In a Phase I trial, 10 patients with advanced low-grade B-cell NHL were given locoregional injection of CD3 \times CD19 bispecific MAb together with anti-CD28 MAbs (59). There was evidence of upregulation of T-cell activity markers by the MAbs and evidence of lymphoma-specific T-cell recruitment in some patients. There were mild to moderate toxicities after the injection of these preparations and 5/10 patients developed HAMA after a single injection (61).

2.2. Peripheral T-Cell Lymphomas (PTCLs) Including Mycosis Fungoides

PTCLs include a number of categories of T-cell lymphomas, which, together, constitute less than 15% of all NHLs in adults (62). In contrast to B-cell NHLs, the pattern of expression T cell-marker antigens is very variable and most subset of PTCLs have their characteristic array of marker expression. Most PTCLs express CD2, CD3, and CD4 and lose one or more of the mature T-cell markers such as CD5 and CD7. A subset of PTCLs (i.e., the angioimmunoblastic T-cell lymphoma) express NK cell markers, e.g., CD2, CD56, CD45RO, and CD43, and lack CD3 and TCR (63).

2.2.1. UNCONJUGATED MAbs IN PTCLs

The chimeric anti-CD4 MAb, cMT412, has been effective against the skin lesions of T-cell cutaneous lymphoma (64). CD5 antigen, expressed by neoplastic T cells of mycosis fungoides, has been targeted by several MAbs including T101 and Leu-1. Unconjugated T101 and Leu-1 MAbs could induce transient response in about 50% of mycosis fungoides patients (65).

2.2.2. RADIOIMMUNOTHERAPY (RIT) OF PTCLs

The results of RIT of T-cell lymphomas and leukemias show an overall response in about 60% of patients but the number of treated patients was small and myeloablative doses were not used (66,67). ^{131}I and ^{90}Y were the radionuclides of choice for these studies. The targeted antigens were CD5 (MAb T-101), CD25 (anti-Tac MAb), and CD2T (expressed by the transformed T cells in human T-cell lymphotropic virus type 1 malignancy).

2.2.3. IMMUNOTOXIN (IT) THERAPY IN PTCLs

Only a very small number of IT therapy trials have been carried out in PTCLs (67). In an early trial, an anti-CD5 MAb-ricin A chain conjugate induced PR in 4/10

patients. Complications were vascular leak syndrome (VLS) and production of blocking anti-IT antibodies in 7/10 patients (68). More recently, an anti-CD7 MAb-dgRA IT induced PRs in 2/11 T-cell lymphoma patients (69). Another conjugate of dgRA with an anti-CD7 MAb, induced PR in 2/11 relapsed T-cell lymphoma patients (70). For IT therapy of cutaneous and other T-cell lymphomas, T-cell leukemias, and Hodgkin's disease, the target antigens of choice were CD6, CD7, IL-2R, and CD25 (51). Response rates (including a few CRs) varied between 10 and 25%. Recently PR was observed in 1/1 cutaneous T-cell lymphoma patient given an anti-T ac(Fv)-PE38 IT (54). The same IT induced PR in 3/4 hairy-cell leukemia and 1/2 adult T-cell leukemia patients. A conjugate of deglycosylated RA with an anti-CD7 MAb, induced PR in 2/11 relapsed T-cell lymphoma patients.

2.3. Hodgkin's Lymphoma (Hodgkin's Disease)

Approximately 7,500 new cases of Hodgkin's disease (HD) are diagnosed every year in the USA (4). Multiple-agent chemotherapy together with extended-field radiotherapy can now induce remission in ~80% of patients in both early-(71) and advanced-(72) stage diseases. Nevertheless, 30–50% of patients with advanced disease at diagnosis succumb to the disease (72) most probably due to the persistence of a small number residual tumor cells that survive after the first line of treatment (73). The goal of MAb-based therapeutic approaches is the elimination of these residual tumor cells.

The cellular origin of HD is controversial (74). The present consensus presumes the Hodgkin and Reed-Sternberg cells (H/R-S cells) to be the malignant-cell population (75). They constitute >1% of the cellular population inside lesions. H/R-S cells express antigens found on activated and nonactivated B-cells (CD19, CD20, CD22, CD79a, and T-cells (CD3, CD4, CD8, and the T-cell receptor [TCR] B chain) (76). HD is especially suitable for MAb-based therapies because the number of tumor cells in lesions is small and the tumors are well-vascularized. IT-therapy after first-line polychemotherapy and radiation therapy has the theoretical advantage that ITs can kill radio- and drug-resistant tumor cells.

The TAAs considered as targets for MAb-based therapy of HD are CD15(Leu-M1), CD21 (C3d/EBV receptor), CD25 (Tac, IL-2 receptor), CD30(Ki-1), CD45 (T-200), CD71 (transferrin receptor, T9) (75), and CD80(B7-1) (77). Of these, CD25 and CD30 have attracted the most interest. Furthermore, the iron-storage protein, ferritin, is found in high concentration in Hodgkin's lymphoma lesions (78). Antiferritin antibodies have been used to target Hodgkin's lymphomas (79).

2.3.1. UNCONJUGATED MABS IN HD

The anti-CD25 humanized MAb, anti-Tac-H, and the anti-CD30 MAb, Ber-H2, failed to show any significant response despite evidence of localization of the MABs in at least 50% of the patient (75).

2.3.2. RIT IN HD

RIT with polyclonal anti-ferritin antibodies labeled either with ^{131}I or ^{90}Y induced response in 15/37 and 18/29 patients. Response was better at higher doses but toxicity, especially bone-marrow suppression, was severe at these dose levels (77,80). Fractionation of doses did not improve results (79).

2.3.4. IT THERAPY IN HD

IT, using an anti-Tac (Fv)-PE38 could induce PR in 1/11 HD patients (54). An IT composed of an anti-CD25 MAb (RFT5) and dgRA induced PR in 2/17 patients (77). All patients given two or more injections developed anti-IT antibodies. There were mild to moderate toxicity including VLS in 5/18 patients.

2.3.5. BISPECIFIC ANTIBODIES IN HD

The administration of an anti-CD16 (a natural killer [NK] cell-associated antigen) antibody \times anti CD30 (a HD-associated antigen) bispecific antibody induced one complete and one partial remission in a group of 15 refractory HD patients (81).

2.4. Leukemias

Leukemias can arise from either myeloid hematopoietic cells (i.e., myeloid or myelogenous leukemias) or from lymphoid precursors (i.e., lymphocytic leukemias). Each category has subcategories based on the differentiation status of the tumor cells and their expression of phenotypic markers. Clinically, each category of leukemias may be either acute or chronic. Not only does the biological behavior of leukemia cells differ between acute and chronic forms of the disease, but they also differ in their expression of TAAs and tumor markers.

Recent progress in the chemotherapy of leukemias has been spectacular. For example, over 95% of children and 80–90% of adults with acute lymphocytic leukemia (ALL) undergo CR after initial therapy. Similar (but somewhat lower) CR rates have been obtained also in myeloid leukemias. However, the overall long-term, disease-free survival in adults is only about 15–30% and there are subgroups of leukemia patients in whom conventional chemotherapy regimens are not effective (82; also *see ref. 83*). There is thus a need to explore and develop novel and more effective therapeutic approaches.

Leukemias are attractive targets for MAb-based therapies because a major proportion of malignant cells in leukemias are free-floating and the relatively large number of lineage-specific and proliferation-related TAAs on their surface are readily accessible to intravascularly administered high molecular-weight therapeutic agents such as MAb-based preparations. Furthermore, the noncirculating leukemia cells reside mostly in well-vascularized tissues such as the bone marrow and spleen and are thus also accessible to MAb-based preparations. However, the rapid binding of administered agents by the circulating tumor cells usually leads to rapid clearance of MAb-based agents so that they can not reach and penetrate into solid organs infiltrated by tumor cells (82). The potential target molecules for MAb-based therapy of leukemias, especially acute leukemias, have been listed by Multani and Flavell (82). They include:

1. CD10 (also known as the common acute lymphoblastic leukemia antigen or CALLA): targeted by MAbs such as J-5;
2. CD5: targeted by MAbs such as Leu1. Leu 1 has been used either alone or in association with MAbs against other T cell-specific antigens.
3. CD25 (IL-2 receptor): targeted by anti-Tac MAb that recognizes the p55 chain of the IL-2 receptor;
4. CD33: targeted by MAbs such as M195; and
5. CD52: targeted by MAbs such as the IgG2b isoform of the CAMPATH-1 family of rat MAbs.

In general, most of the unconjugated MAb could induce rapid but transient decrease in the number of targeted cells in circulation, but there was no sustained response.

2.5. Acute and Chronic Myeloid Leukemias (AML and CML)

AML is the most common variant of acute leukemia in adults, constituting about 80% of adult acute leukemias. CML accounts for ~15% of all patients with leukemia (4). CML is a clonal proliferative disorder of pluripotent hematopoietic progenitor cells with a specific chromosomal abnormality (i.e., reciprocal translocation between the long arms of chromosomes 9 and 22). This translocation creates a new *bcr-abl* fusion gene, the products of which are constitutively activated tyrosine kinases, which, in their part, influence in an unregulated manner, a number of cellular functions including proliferation, differentiation, cell-cell interactions, and apoptosis (84). These tyrosine kinases and other molecules in their signaling pathways offer excellent targets for designing novel therapeutic agents for CML. At present CD33 is the target of choice in myeloid leukemias because CD33 is expressed by myeloid progenitor cells and on AML cells of some patients, but not by the pluripotent stem cell (82).

2.5.1. UNCONJUGATED MABS IN AML AND CML

An early trial with four murine MAb against myeloid differentiation antigens could only elicit transient decrease in the number of circulating leukemia cells without any PR or CR (85). An unconjugated anti-CD 33 MAb, M195, had no antitumor effect in 10 AML patients (86). The humanized M195 MAb could induce CR only in 2/35 patients with refractory or relapsed AML, even though there was persistent saturation of the circulating leukemia cells at least for 4 wk (87). In another trial of HuM195 in acute promyelocytic leukemia, patients, who were in *trans* retinoic acid and/or chemotherapy-induced CR were given HuM195 along with further chemotherapy. Results were inconclusive (88). HuM195 was well tolerated in all the trials. CD44, a glycoprotein, is expressed on blast cells from most AML patients. Several anti-CD44 MAb can induce differentiation in AML blast cells in vitro. No clinical trial of anti-CD44 MAb has been reported yet (89,90). p75/AIRM1 is a sialoadhesion family surface molecule that is normally expressed on NK cells and has homology with the myeloid-cell antigen CD33. p75/AIRM1 is also expressed on myelomonocytic-cell precursors and CML cells. Anti-CD33 or anti-p75/AIRM1 MAb could induce marked inhibition of proliferation of CML cells in vitro (91). No clinical trial of anti-p75/AIRM1 MAb has been reported.

2.5.2. RIT IN AML

2.5.2.1. Radiolabeled Anti-CD33 MAb. ¹³¹I-Conjugate of MAb M195, was given to 25 patients including 16 AML patients and one patient with blast transformation of CML. There was significant eradication of blast cells in the peripheral blood and bone marrow in most patients. Three patients had complete response (92). Recently, Jurcic et al. treated 18 relapsed or refractory AML or chronic myelomonocytic leukemia patients with ²¹³Bi-linked to huM195. Ten patients had reduction of leukemic cells in the peripheral blood and 13 had reduction in the number of blast cells in the marrow (93). Pharmacokinetic and dosimetric studies with this conjugate are in progress (94). Results of biodistribution studies of radiolabeled huM195 demonstrated 1000-fold higher localization of radioactivity in liver, spleen, and bone marrow than in the rest of the body of AML patients (94).

2.5.2.2. Radiolabeled Anti-CD45 MABs in AML. CD45 is present in relatively large copy numbers on the majority of lymphocytic as well as myeloid leukemias (83). After a biodistribution study and Phase I evaluation of an ^{131}I labeled anti-CD45 MAb (BC8) (95), a phase II trial on the efficacy of ^{131}I -BC8 is currently in progress (83).

2.5.3. ITs IN AML

A ricin-containing IT of an anti-CD33 MAb was found to be too toxic for the continuation of a clinical trial (82).

2.5.4. DRUG-MAB CONJUGATES IN AML

In a Phase I trial of CMA-676 (an immunoconjugate in which a humanized anti-CD33 MAb is linked to calicheamicin gamma 1-1) in 40 patients with refractory or relapsed AML, leukemic cells were eliminated from the blood and bone marrow of 20% of treated patients. Toxicity was primarily hematological but was not dose-limiting (96).

2.6. *Acute Lymphocytic Leukemia (ALL)*

Despite their common morphologic and immunophenotypic features, there is a striking difference in the outcome of childhood and adult ALL. The outcome rapidly worsens with the age of the patient (4). For example, the cure rate of adult ALL in the last decade has been 30–40%, which is half the cure rate of childhood ALL (83). Approximately 75–85% of ALL are of B-cell origin, displaying CD10(CALLA), CD19(B4), CD20, and IG gene rearrangements. The rest of ALLs are of T-cell origin and express CD3, CD7, and CD52 (83). Some ALL blast cells co-express myeloid markers such as CD13 and CD33. For MAb-based therapies to be effective, the target antigen(s) should be present on at least 30% but preferably 50% of the blast cells.

2.6.1. UNCONJUGATED MABS IN ALL

CD20 is expressed by >30% of the leukemic cells by the majority of comparatively mature B-cell CLL and by about one-third of B- precursor ALL (83). ALL is thus a good candidate for anti-CD20 MAb therapy. An unconjugated humanized anti-CD52 MAb (CAMPATH-1H) has been effective in T-cell prolymphocytic leukemia. CD 52 is expressed by most lymphoblasts, but by a higher proportion of T-lymphoblasts than B-lymphoblasts. Eleven of 15 patients, given CAMPATH-1H, had a major remission including CR in nine patients. However as is usual with this MAb, treatment resulted in significant toxicity including severe bone-marrow failure in two patients (97). In another trial, Campath-1H induced PR in 1/5 CD52⁺ ALL patients (98). Unconjugated anti-CD25 MABs have also produced PRs and CRs in a proportion of adult T-cell leukemia patients (99).

2.6.2. RIT IN ALL

A humanized anti-Tac (i.e., CD25) MAb- ^{90}Y conjugate was given to 17 patients suffering from adult T-cell ALL. Eleven patients had sustained PR or CR (100).

2.6.3. RIT + WHOLE-BODY RADIATION + CYCLOPHOSPHAMIDE + HLA-MATCHED BONE-MARROW TRANSPLANTATION

Twenty-five patients with advanced AML and nine with advanced ALL were subjected to the aforementioned regime. Seven of the AML patients were surviving tumor-free 15–89 mo post-bone marrow transplantation. Three of the ALL patients were surviving tumor-free 19–16 mos post-transplantation (101).

2.6.4. IT THERAPY IN ALL

2.6.4.1. CD19-Based ITs. CD19 is associated with the Src family of protein tyrosine kinase (PTK) and is a constituent of the membrane-associated CD19-PTK complex that acts as an endogenous, p-53- and Bcl2-independent regulator of apoptosis (102). CD 19 is expressed in high copy numbers by the leukemic cells of the majority of ALL patients but not by bone-marrow stem cells (102). Seven children and eight adult patients of CD19+ B-cell ALL and one patient of B-cell CLL were treated with a conjugate containing the anti-CD19 MAb, B43, and the PTK inhibitor, Genistein. There were two transient responses and one durable CR. There was considerable toxicity including VLS in two patients. Three of nine patients developed human antimouse immunoglobulin antibody (HAMA) response (103). A conjugate containing the same MAb and pokeweed antiviral protein induced CR in 10/15 and PR in 2/15 relapsed childhood ALL patients. However the patients were simultaneously given a four-drug reinduction chemotherapy regimen (104). A bRA conjugate of the anti-CD19 MAb, B4, had no demonstrable effect in 46 patients with CD19+ ALL (105).

2.7. Chronic Lymphocytic Leukemia (CLL)

CLL is characterized by progressive accumulation of monoclonal B lymphocytes developmentally arrested between pre-B cell and mature B cell. CLL constitutes ~30% of all adult leukemias in the Western world (106). CLL cells express pan-B-cell markers such as CD19 and CD20, the activation marker CD23, and the T-cell marker CD5. The malignant B-cell clones in CLL bear scanty amounts of sIg (107). However, the expression of phenotypic markers in some subsets of CLL differs from this general pattern (107). MAb-based therapies of CLL have mostly targeted CD20 and CD52 using rituximab and campath-1H MAbs, respectively.

Even though the introduction of purine analogues such as flutrabine has improved the outcome of CLL, response to other currently available therapies is poor when the disease becomes refractory or does not respond *ab initio* to flutrabine. This underlines the need for developing novel treatments for CLL.

2.7.1. UNCONJUGATED MAbs IN CLL

2.7.1.1. Rituximab. Even though CD20 is expressed by CLL cells of 95% of patients, the density of CD20 expression on CLL cells is usually very low (108). It is therefore not surprising that early studies (109,110) had very low response rates, i.e., from 12–13%, at once a week dose of 375 mg/mxm for 4 wk. This could have been due to the difficulty in achieving and maintaining adequate plasma concentration of the MAb (24,111,112). In two subsequent dose-escalation studies, response rate increased to 39% and 45% with subsequent reduction in blood-cell counts and organ involvement with the exception, in most cases, of bone-marrow involvement (113,114). A number of clinical trials with high doses of rituximab and a combination of rituximab and chemotherapeutic agents, especially flutrabine and cyclophosphamide, are in progress (111). The rationale for the combination therapy is based on the observation that rituximab chemosensitizes lymphoma cells (115).

2.7.1.2. Campath-1H. The anti-CD52 MAb campath-1H has demonstrated significant activity against untreated (116) as well as previously treated CLL (117–120). In the largest Phase II trial containing 29 previously treated patients there was 4% CR and 38% PR (119). However, in most patients there was no response in lymph-nodal

lesions. The limiting problem with campath-1H is its severe immunosuppressive effect, leading to susceptibility to infections (111). Reducing the dose and duration of campath-1H administration has reduced toxicity, yielding a PR of 33% in flutrarabine refractory CLL (120).

2.7.1.3. Anti-CD25(Tac) MAbs. An anti-Tac MAb induced complete response in 10% of patients. Response lasted from 2 mo to 3 yr. All T cell-specific MAbs induced profound immunosuppression and complications such as pneumocystis pneumonia and Kaposi's sarcoma.

2.7.1.4. ID10 Antigen and HuID 10 MAb. Hu ID 10 MAb binds to an epitope associated with a variant of HLA-DRb chain on the surface of malignant B-lymphocytes. It is expressed on malignant B-lymphocytes of ~50% of CLL and NHL patients. Responses have been noted in a Phase I trial (111,121).

2.7.2. IT THERAPY OF B-CELL CLL

B-cell CLLs have been targeted via CD19 or CD22 by dgA or truncated PE containing ITs. CR was obtained in 1/42 patients (51). Recently, CR was obtained in 1/8 CLL patients after treatment with an anti-Tac (Fv)-PE38 IT (50).

2.8. Indirect MAb-Therapy of B-Cell Malignancies: Neutralization of Stimulatory Cytokines

In those B-cell malignancies that are thought to be driven by IL-6 (e.g., aggressive B-cell lymphomas in HIV-positive patients and multiple myeloma), anti-IL-6 MAbs have been successfully used to lower the serum level of IL-6. This mainly alleviated symptoms such as cachexia and fever (122,123).

2.9. Plasma-Cell Malignancies: Multiple Myeloma (MM), and Waldenstrom's Macroglobulinemia (WM)

MM and WM are malignant proliferation of plasma cells or B cells accompanied by the presence in the serum and/or urine of monoclonal Ig or Ig fragments. Every year there are ~ 14,000 new cases of MM and ~ 1,500 new cases of WM in the USA, making plasma-cell malignancies the second most common malignancy in that country (124). Even though flutrarabine and other purine analogues can induce from 40–80% response after initial therapy and 40–50% response in salvage therapy, eventual chemotherapy fails and patients succumb to the disease (124).

The clonal origin of the malignant cells in MM and WM is uncertain. The clonogenic cells may be plasma cells, B cells, pre-B cells, or all the three (125). However, the potential targets for MAb-based therapy of MM and WM are: The idiotypic Ig of the malignant clone, CD19, CD20, CD38, CD54, CD138, HM1.24, and the MUC1 core protein (125). In both MM and WM malignant clonotypic B cells are found in the circulation (125) and they have to be eradicated for therapy to be effective.

Anti-idiotypic MAbs are not likely to be effective in MM and WM because of the large amounts of free idiotypic proteins in the serum of these patients. Both CD19 and CD20 are B cell-specific antigens that are expressed from early B-cell to mature B-cell stage. Both are only minimally expressed on malignant clones of MM but CD19 is expressed by 75–100% of malignant clones of WM and the expression of CD20 by malignant plasma cells in MM can be enhanced by IFN- γ (125). The usefulness of CD38 is limited because it is also expressed on normal plasma cells, pre-B cells, T

cells, and CD34+ hematopoietic progenitor cells. Even though CD54 (ICAM-1) is strongly expressed on MM plasma cells, its usefulness is also limited because it is also expressed on activated T cells, endothelial cells, epithelial cells, and bone-marrow stromal cells. Furthermore there may be higher than normal levels of soluble ICAM-1 in the serum of MM patients. CD138 (syndecan-1) is another adhesion protein that is strongly expressed on MM cell lines but like ICAM-1, its usefulness is also limited because anti-CD138 MABs also bind to normal plasma cells as well as epithelial and endothelial cells. There is evidence that the MUC1 core protein is selectively expressed by MM plasma cells and B cells. The transmembrane protein, HM1.24 antigen, has been identified on MM plasma cells and myeloma cell lines. Anti-HM1.24 MABs have demonstrated tumor-specific localization and antitumor effect in MM-xenograft models (126). The humanized anti-HM1.24 MAB mediated tumor inhibition via ADCC (127).

2.9.1. UNCONJUGATED MABS IN MM

2.9.1.1. Multiple Myeloma. In a preliminary report, 1 PR was obtained in 18 MM patients treated with unconjugated rituximab (124,125). In another study, in which melphalan and prednisone were added to rituximab, 5/22 patients had a response to rituximab, before the administration of the chemotherapeutic agents (128). There was no significant response in four stage III MM patients given unconjugated rituximab (129).

2.9.1.2. Waldenstrom's Macroglobulinemia. Several preliminary studies indicate that rituximab can induce relatively short-term remissions in WM (*see ref. 125*).

2.9.2. IT THERAPY IN MM

There was no clinical response in 5 MM patients after treatment with a blocked ricin-linked anti-CD19 MAB (130).

2.9.3. RIT FOR EX-VIVO BONE MARROW PURGING IN MM

²¹³Bi-linked anti-syndecan-1 MAB, B-B4 (131), and ¹³¹I-linked anti-MUC1 MAB, MA5 (132) were found to be suitable for the specific elimination of MM cells from bone marrow.

2.10. Hazards and Limitations of Anti-Lymphocyte MABs

2.10.1. ANTI-CD20 MABS

Rituximab has been offered in the market as a nontoxic alternative to chemotherapy (133). Indeed, in most cases the adverse effect profile of rituximab has been very benign. Infusion-related symptom complex, consisting of fever, chill, and rigors, usually occurs within 0.5–2 h of the first infusion in ~50% of patients given rituximab. The symptoms are mostly self-limited but sometimes necessitate temporary interruption of rituximab infusion along with some supportive measures. Subsequent infusions of the MAB are usually well-tolerated. More severe infusion-related adverse reactions like severe bronchospasm and hypotension have been reported in ~2% of patients. HAMA response has been very infrequent probably because of the anti-B-cell activity of the MAB. Furthermore, immunosuppression by rituximab has been much less severe than that induced by the anti-CD52 MAB, Campath-1H (17).

However, postmarketing monitoring for adverse reactions has now revealed several hazards and limitations of rituximab, as summarized below.

1. Tumor-lysis (TLS) and cytokine-release (CRS) syndromes: A few CLL (*134*) and NHL patients (*135*) with high lymphocyte count in the peripheral blood developed elevated levels of phosphate, uric acid, and LDH from massive necrosis of tumor cells usually soon after the first infusion of rituximab at 375 mg/m² dose levels. A gradual step-up of rituximab dose may delay the onset and attenuate the severity of TLS and CRS (*135*). Similar TLS has been observed after chemotherapy of rapidly proliferating lymphomas (*136*), leukemias (*137*), and solid tumors (*138*).

In cytokine-release syndrome, patients with high peripheral-blood lymphocyte counts develop within ~2 h of the first MAb infusion severe fever, chill, rigors, nausea, vomiting, hypotension, and bronchospasm along with elevated levels of serum TNF- α , IL-6, and liver enzymes. There is also usually prolongation of prothrombin time (*134,135*).

2. Loss of CD20 expression: Loss of CD20 expression has been documented in one patient after two courses of therapy with rituximab (*136*).
3. Acceleration of disease: There is also one report about the acceleration of multiple myeloma after treatment with rituximab (*137*).

2.10.2. HAZARDS OF OTHER MABS

As already stated, Campath-1H induces profound immunosuppression, especially the downregulation of T cell-mediated immunity, which predisposes to opportunistic infections. TLS and CRS have been observed after therapy with the anti-CD52 MAb, Campath-1H (*120*), anti-CD5 MABs such as T101 (*138*), and the anti-lymphoma MAb Ab89 (*139*).

3. SOLID TUMORS

The difficulties in the use of MAb-based therapies in solid tumors, especially the problems associated with the accessibility of targeted tumor cells to circulating antibodies, have already been discussed in the preceding chapter. However results from experimental models and from patients clearly show that RIT can deliver more radioactivity to the target tumor tissue than to normal tissues. A recent pharmacokinetic and biodistribution study in patients with advanced breast cancer has demonstrated that RIT may deliver between 3 and 50 times the dose of radiation to target tumor tissues throughout the body compared to the normal tissue doses (*145*).

4. BREAST CANCER

There has been a resurgence of interest in MAb-based therapy of solid tumors, because of the impressive results of the trials on the effectiveness of the recombinant humanized anti-HER2/neu MAb, 'Herceptin,' in metastatic breast cancer, when the lesions overexpress HER2/neu (*146*). The amplification of the protooncogene c-erbB (also known as HER-2 or neu because this gene was identified independently by different groups) is one of the earliest abnormality seen in breast-cancer cells. This gene codes for a 185 KD transmembrane protein with tyrosine kinase activity and has about 50% amino acid homology with EGFR. This protein is overexpressed, with or without gene amplification, in about 60% of ductal carcinomas and 20–30% of invasive breast cancer. HER-2/neu is an excellent target because: 1) it is located on the cell surface; 2) in lesions that express HER-2/neu, the antigen is present on a large proportion of cells; and 3) metastases of positive lesions also express the antigen.

In Phase I and Phase II trials, response rates varied between 12% and 15% (147–147c). There is also evidence that this MAb potentiates the antitumor effect of a number of chemotherapeutic agents including cisplatin, carboplatin, anthracyclines, cyclophosphamide, paclitaxel, docetaxel and vinorelbine (148–148f).

However, long term follow up has revealed cardiotoxicity in 4.7% of patients given trastuzumab alone. Cardiotoxicity is considerably increased (i.e. 27%) in patients given trastuzumab and chemotherapy especially when given trastuzumab + an anthracycline and cyclophosphamide (*see ref. 148g*).

Other potentially targetable breast cancer-associated antigens and the available results of clinical trials, based on MAbs against these antigens, are listed in ref. (149). The targeted antigens include EGFR, HER-2/neu, CEA, and several mucin antigens like tumor-associated glycoprotein 72 (TAG 72), Lewis- γ antigen, muc-1, and L6 antigen. Most of these were MAb-based Phase I trials. The MAbs had tolerable toxicity. The chimeric antiCEA MAb, T84.66, showed good localization in CEA producing metastatic lesions. There was no evidence of any significant tumor inhibition by any MAb other than rhu MAb, HER2/neu.

4.1. RIT

A Phase I study using 90-Y linked, chimeric anti-CEA MAb, T84.66 demonstrated good tumor localization of radioactivity at metastatic breast-cancer lesions without any significant tumor inhibition (150). However, the result of a Phase I study using 90-Y- MAb 170H.82 conjugate on metastatic breast cancer patients appears to be therapeutically more promising (151).

4.2. Drug-Antibody Conjugates

In a Phase I trial on a mixed bag of carcinoma (including breast carcinoma) patients, using an immunoconjugate consisting of the chimeric anti-Ley antibody, BR 96, and doxorubicin, a prolonged serum level of the drug could be maintained. Depositions of the antibody and doxorubicin could be seen in several samples of biopsied tumor tissue. Objective clinical responses were observed in 2/66 patients. Acute hemorrhagic gastritis, caused by the carrier antibody, was the dose-limiting toxicity but there were no significant hematological or cardiac toxicities (152). In a Phase II trial in patients with metastatic breast carcinoma, there was only one partial response in a patient with liver metastases out of the 14 patients who received the conjugate, but there were three partial and one complete responses in the nine patients who had received doxorubicin alone (153). It appears that this conjugate could not deliver adequate amounts of doxorubicin to the target tumor tissue. Dose escalation was not possible because of the toxicity of the carrier MAb. MAbs that do not react with the gastro-intestinal epithelium may be better carriers.

4.3. Immunotoxin

A conjugate of MAb B3 (that binds to a carbohydrate moiety of the Ley family) and the truncated PE (PE 38) produced 1 CR and 1 PR in patients with disseminated breast and colon cancers, respectively (154).

4.3.1. BISPECIFIC ANTIBODIES

A humanized Fab anti-CD64 \times antiHER-2neu (MDX-H210) marketed by Medarex Inc. has produced some “promising antitumor effects” in breast cancer patients refractory to other methods of treatment (155).

5. COLORECTAL CANCER

Colorectal cancers were the focus of early studies on the effectiveness of MAb-based therapeutic approaches. The targeted antigens include TAG 72, the 40–47 kD extracellular-adhesion glycoprotein Ep-CAM, and CEA. The results of clinical trials are in (156,156a). The most promising results have been obtained with unconjugated anti-Ep-CAM MAb, 17-1A (156b). A pilot study in Duke's C stage colon cancer, after prior curative surgery, led to 30% reduction in death rate and 27% reduction in recurrence rate. The results of this study are notable because of the following: 1) the 17-1A antigen is widely expressed in normal tissues, 2) injections of this murine MAb was continued even though 80% of the patients developed HAMA without any major toxicity and without affecting the therapeutic outcome, and 3) the MAb was effective only in minimal residual disease. Larger trials are now under way. The precise mode of action of this murine MAb is not known but has been postulated to be due to ADCC (157) or immunization via the idiotype-antiidiotype network (158).

Combination of MAb 17-1A with GM-CSF and interleukin-2 (156e) or with gamma interferon (156f) did not add to the effectiveness of MAb 17-1A alone. Combination of 5FU with this MAb did not reveal any additive toxicity (156b).

5.1. RIT/IT/ICT

Radioimmunotherapy using a ^{131}I linked, anti-Tag 72 MAbs (158a) or ^{131}I labeled A33 MAb (against a high molecular-weight glycoprotein expressed by both normal and malignant gastrointestinal epithelium) (158b) did not produce any objective improvement. The maximum dose delivered was 5–6 cGy of tumor-absorbed dose. Most patients, given the higher doses required stem-cell support to overcome dose-limiting bone-marrow toxicity. To avoid myelosuppression, Meredith et al. linked MAb 17.1 with the low-energy Auger electron emitter ^{125}I up to a dose of 250 mCi. There was no myelosuppression but there was also no response (158c). Systemic administration of an immunotoxin constructed with ricin-A chain and MAb 791t/36, led to the reduction in the size of liver metastases in 2/17 patients (158d). A group of eight patients were treated with the chemotherapeutic agent neocarsinostatin linked to MAb A7. Two had PR and two other had minor response (158e).

5.2. ADEPT

A conjugate containing the F(ab)₂ fragment of a murine anti-CEA MAb and the bacterial enzyme carboxypeptidase G2 was given to patients with advanced colon cancer who did not respond to conventional therapy along with a benzoic acid mustard pro-drug. After three cycles of treatment, five of the eight patients had >50% regression in their identifiable tumor masses (159). All non-immunosuppressed patients developed antibodies against both the components of the conjugate by the tenth day after conjugate injection. There was also myelosuppression in all patients. Myelosuppression was the predominant complication also in another trial in which only a single injection of the same conjugate was administered (160).

5.2.1. BISPECIFIC ANTIBODIES

A bispecific antiCD3 \times anti17-1A (antiEpCAM or EGP2) antibody could significantly reduce the overall death rate in a group of 189 patients with resected Duke C colorectal carcinoma (161).

6. GENITO-URINARY CANCERS

6.1. *Immunotoxins (ITs)*

Local instillation of TP40, an IT consisting of TGF- α and truncated PE, led to histologically confirmed improvement of cancer *in situ* of bladder (162).

6.2. *Bispecific Antibodies*

Intravenous administration of a humanized Fab anti-CD64 \times anti-EGF-receptor bispecific antibody (MDX 447, marketed by Medarex Inc.) has produced “promising anti-tumor effects in patients with refractory cancers of the kidney, bladder, prostate, breast, ovary and head and neck” (161).

7. OVARIAN CANCER

A number of MAbs have been used in the treatment of ovarian cancer (156). Unconjugated MAb, L6, which binds to a number of carcinomas, did not produce any response.

7.1. *RIT*

Intraperitoneal administration of ^{90}Y -linked MAb HMFG1 (directed against polymorphic epithelial mucin) increased survival (compared to historical controls) only in the adjuvant setting (162b). ^{186}Re -linked MAb NR-LU-10 could induce response only in a cytoreductive surgery or chemotherapy (162c). ^{177}Le -linked MAb CC49 could induce PR only in an occasional patient with macroscopic disease in spite of good tumor localization of radioactivity (162d).

A single patient, intraperitoneally given *Pseudomonas* exotoxin linked MAb OVB3, developed encephalopathy without any tumor inhibition (156).

7.2. *Bispecific Antibodies*

Intraperitoneal administration of an anti-CD3 \times anti-folate receptor antibody, autologous T lymphocytes, and IL-2 in a group of 19 patients with advanced ovarian cancer led to 3 complete response, 4 partial response, and 7 stable disease (163).

A bispecific MAb, MDX-210 with specificity for Fc receptor (FcR) and HER2/neu (that can be overexpressed in ovarian cancer) led to a mixed response in 1/6 stage 3 or stage 4 patients (163a).

8. CANCERS OF THE LUNG

8.1. *Immunotoxin*

An IT consisting of EGF and the truncated diphtheria toxin (DT), DAB389, was found to be effective in an EGFR+ lung cancer-patient (164).

9. MELANOMA

Antibody-defined melanoma antigens are mostly differentiation antigens and include ganglioside antigens GD2, GD3 (the most widely expressed melanoma-associated antigen) and GM2, p97/gp95 antigen (or melanotransferrin) and the high molecular-weight melanoma-associated antigen, p240. These antigens are also present in limited amounts in some normal tissues. The unconjugated MAb R24 against GD3 was

evaluated in several different Phase I trials (164a–164g). Inflammatory reaction was seen around bulky lesions in most patients. Partial response was seen in small proportion of cases. There was spectacular remission lasting over 6 yr in a patient with melanosis of the meninges (164d). Deposit of R24 could be detected in most of the lesions examined. Similar results were obtained with several MABs against GD2 and GD3 (164h–164j). Unconjugated MABs against p97 and p240 had no effect on melanoma lesions (164k).

9. IMMUNOSCINTIGRAPHY

MABs to p95 and p240 have been widely investigated for the detection of melanoma metastases after linkage to 111-In, ¹³¹I, or ¹³⁵I. Between 19 and 74% of known lesions could be detected by scintigraphy.

9.1. Unconjugated MABs Along With Other Agents

Addition of the unconjugated anti-GD3 MAB, R24, to cisplatin or the radioprotective agent, WR-2721 did not add to the effects of cisplatin or WR-2721 alone (165). Addition of GM-CSF to MAB R24 did not improve the outcome (166) but the addition of M-CSF induced several mixed responses (167). Co-administration of IL-2, in high doses, with R24 (168) induced partial response in 10/23 melanoma patients in one treatment group and partial or minor responses in 3/20 patients in another group (169). However, lower doses of IL-2 with another anti-GD3 MAB, MG-22, did not elicit any response (170). Coadministration of recombinant TNF- α and R24 did not produce any beneficial effect. (171).

9.2. RIT/Immunoscintigraphy

In melanoma patients given IFN- α 24 h before the administration of ¹¹¹In-labeled anti-melanoma MAB 96.5, immunoscintigraphy led to a threefold increase in radioactivity in melanoma lesions but not in any normal tissue compared to control patients who were not pretreated with IFN- α . It appears that pretreatment with IFN- α may increase tumor-specific deposition of anti-TAA MAB by inducing increased TAA expression (172).

9.3. Immunochemotherapy (ICT)

In the first report on the use of immunoconjugates in cancer patients, a group of 13 melanoma patients with disseminated disease were intravenously injected with the alkylating agent chlorambucil linked to polyclonal antimelanoma antibodies. Objective tumor regression was seen in two patients and five others showed stabilization of cutaneous, nodal, and visceral lesions and significant prolongation of survival compared to a group that received chemotherapy alone (173). Antimelanoma antibody adriamycin or mitomycin conjugates produced only mixed results (173a,173b).

9.4. Immunotoxin (IT)

In two separate studies a total of more than 200 patients were given XOMAZYME-MEL, an immunotoxin, constructed with an IgG2a MAB against the high molecular-weight melanoma-associated antigen and the A chain of ricin. The preparation had acceptable toxicity. There were several mixed responses and a few complete

responses. Most patients produced antibodies to the preparation leading to its rapid clearance (174,175).

10. TUMORS OF THE CENTRAL NERVOUS SYSTEM

10.1. Immunotoxins (ITs)

Transferrin receptor (TfR) is expressed by many tumors but not by any normal tissue (at least in any significant number) except liver. The TfR of CNS tumors have been targeted either by anti-TfR MAbs or human Tf-based conjugates. A conjugate consisting of the anti-TfR MAb 454A12 and rA chain of ricin, could clear (after intraventricular administration), 50% of malignant cells from the cerebrospinal fluid (CSF) of approx half the patients (176). In another trial, an IT consisting of a mutant DT and Tf was directly instilled into the tumors of 18 patients. There were 2 CRs and 7 PRs (176a). Several ongoing clinical trials in high-grade glioma patients are evaluating the effectiveness of the intratumoral administration an IT consisting of PE and a circularly permuted variant of IL-4 that has high affinity for its receptor (177). High-grade gliomas overexpress IL-4R.

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