



William Wolk. *Elvis*. Oil on canvas, 24" × 30".

Monoclonal antibodies, either as single agents or combined with chemotherapy or autologous stem cell transplantation, can be effective therapy for lymphoid malignancies.

Monoclonal Antibody Therapy With Autologous Peripheral Blood Stem Cell Transplantation for Non-Hodgkin's Lymphoma

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Background: *With the introduction of novel monoclonal antibody products into the clinic, significant new strategies are being developed to improve upon existing treatment for non-Hodgkin's lymphoma.*

Methods: *Monoclonal antibodies are being used alone, in combination with chemotherapy, or as adjuncts to autologous bone marrow transplantation for the purpose of purging bone marrow of neoplastic cells.*

Results: *Monoclonal antibodies when used in vivo in conjunction with autologous bone marrow transplantation have been relatively well tolerated. Results from several trials seem to demonstrate a therapeutic benefit for the use of such combinations.*

Conclusions: *Before these agents can be included in standard bone marrow transplantation regimen, long-term survival outcomes need to be obtained from randomized trials. We review the results from recent trials using monoclonal antibodies in conjunction with autologous stem cell transplantation for the treatment of non-Hodgkin's lymphoma.*

Introduction

Monoclonal antibody (MAb)-targeted anticancer therapy became a reality approximately a quarter of a century ago following the discovery of the hybridoma technology.^{1,2} The first antibodies studied were unmodified murine, rat, or rabbit antibodies. Treatment with murine antibodies is associated with development of human antibodies to mouse antibodies (HAMA) that results in shortened serum half-life and

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prevents repeated dosing, inadequate fixation of human complement, and the inability to fully activate host antibody-dependent cellular cytotoxicity (ADCC).^{3,4} The development of “chimeric” or “humanized” antibodies has been one of the key advances to the use of MAb-based therapy. In addition to their low immunogenicity, humanized antibodies have an increased ability to activate the complement cascade system and ADCC. Another important advance in MAB technology has been the ability to engineer radioactive isotope-conjugated antibodies.

The development of MAbs has led to new strategies for the treatment of lymphoma, including their use *in vivo* in conjunction with autologous stem cell transplantation (ASCT).

Autologous Stem Cell Transplantation With Rituximab *In Vivo* Purging

For patients with intermediate and high-risk non-Hodgkin's lymphoma (NHL), several clinical trials, including the Parma study, have demonstrated the superiority of high-dose therapy with bone marrow transplantation (BMT) when compared to salvage chemotherapy for patients with aggressive NHL.⁵ Unfortunately despite this advance, many patients ultimately relapse and die from their disease.⁶ The causes of relapse include the persistence of residual neoplastic cells despite high-dose chemotherapy and re-introduction of malignant cells into the host with the stem cell graft. A number of strategies have been developed attempting to circumvent both problems and include dose-intensification, introduction of novel chemotherapeutic agents and the use of MAb targeted at the neoplastic cells for the purpose of purging of the autologous bone marrow or peripheral blood graft.

Improved disease-free survival was seen in patients with follicular lymphomas who underwent autologous bone marrow transplantation (ABMT) after *in vitro* purging of their marrow graft using MAbs.⁷ Autologous marrow grafts from 114 patients with B-cell malignancies were purged *in vitro* with a cocktail of anti-B-cell MAbs (anti-B, -B5, and -J5). The efficacy of the marrow treatment was assessed by the sensitive polymerase chain reaction (PCR) of marrow specimens before and after the purge. A >3 log reduction of lymphoma cell contamination was achieved with purging, and in 57 patients (50%), no residual neoplastic cells could be identified. Detection of residual lymphoma cells in marrow after purging correlated directly with a 39% relapse rate after a median follow-up of 23 months vs a 5% relapse rate in patients whose graft showed no residual lymphoma ($P < .00001$). Although long-term fol-

low-up indicates that some of these remissions are durable, late relapses are still being observed.^{7,8}

As *in vitro* purging strategies have been largely unsuccessful at completely eliminating neoplastic cells from the graft, treating patients with tumor-specific MAb *in vivo* is being investigated as a potentially more effective way of reducing the number of lymphoma cells contaminating the peripheral stem cell graft. In addition, the use of MAB prior to high-dose therapy and ABMT could potentially sensitize neoplastic cells to chemotherapy. The feasibility of treating patients *in vivo* for the purpose of purging malignant cells was demonstrated by Dyer et al⁹ who used the Campath-1H antibody in patients with chronic lymphocytic leukemia who had residual disease after being treated to maximum response with purine nucleoside analog. The Campath antibodies are a group of “humanized” MAbs that recognize the CD52 antigen. The CD52 antigen is abundantly expressed (up to 5×10^5 molecules per cell) on T and B lymphocytes and on monocytes.¹⁰ In this trial, 5 patients achieved hematologic and histologic complete remission following treatment with Campath, and 1 patient had minimal focal residual disease. These responses allowed for subsequent peripheral blood stem cell harvests. Clinical trials using Campath for *in vivo* purging in combination with ABMT are currently being done, including a phase II study within the Eastern Cooperative Oncology Group (E8998).

Given its efficacy as a single agent or in combination with chemotherapy, as well as its minimal toxicity and non-cross-resistance mechanism with chemotherapy, rituximab has emerged as an ideal candidate for incorporation into ABMT regimens. Several studies using rituximab as an *in vivo* purging agent have reported the ability to render a graft negative of tumor cells by PCR while showing no evidence of adverse effects on the collection of stem cells or on engraftment (Table 1).¹¹⁻¹⁶ Several groups published their experience with combination of rituximab and autologous peripheral blood stem cell transplantation. Buckstein et al^{11,17} showed that *in vivo* purging with rituximab followed by posttransplantation administration of rituximab led to complete molecular remission in patients with relapsed low-grade lymphoma. Fourteen patients were treated with rituximab *in vivo* prior to high-dose chemotherapy and ASCT. Patients were also treated with a 2-week course of rituximab starting on weeks 8 and 24 posttransplantation. All patients were evaluated by PCR for the presence of the t(14;18) translocation. Two patients were still positive prior to the first course of rituximab consolidation, and by the second course of rituximab, all patients had become negative for the translocation. All of the 7 evaluable patients who were positive for the translocation by

PCR eventually converted to a negative test after the transplantation.

More recently, Magni et al¹³ reported on 15 patients with relapsed indolent lymphoma or mantle cell lymphoma who were treated with a combination of rituximab and high-dose chemotherapy. These patients were treated with 2 doses of rituximab given following each cycle of high-dose chemotherapy for a total of 6 doses. Reinfusion of ASCT occurred 24 hours after each of the 2 cycles of the treatment combination (chemotherapy/Mab) for a total of 3 reinfusions. While the antibody was administered after chemotherapy, given the tight sequencing of the subsequent chemotherapy, it is likely that significant levels of rituximab were present at the time of the next chemotherapy. These patients were compared to a prospective cohort of 10 patients who underwent the same therapy without the use of rituximab. Of note, ex vivo purging using anti-CD19 MAbs was performed in those patients not treated with rituximab and whose grafts were still positive by PCR despite high-dose chemotherapy. Following in vivo purging with rituximab, 93% of patients had a PCR-negative graft compared with 40% of the patients in the control arm ($P=.007$). Even after ex vivo purging, the proportion of PCR-negative patients in the rituximab group was 93% compared with 80% in the control group. A higher

yield of CD34-positive/PCR-negative cells was obtained from the patients in the rituximab arm. Finally, with a short follow-up of 10–14 months, 7 (70%) of 10 patients in the control arm and 14 (93%) of 15 patients in the rituximab arm continued to be free of clinical and molecular disease.

Similar results have been reported elsewhere.¹² In an effort to exploit the known in vitro synergy with chemotherapy, 25 patients with low-grade lymphoma or mantle cell lymphoma received 375 mg/m² of rituximab 3 days prior to high-dose cyclophosphamide to mobilize stem cells. Filgrastim was administered subcutaneously at 10 µg/kg per day starting on the day after chemotherapy and continuing until completion of leukapheresis. Successfully mobilized patients subsequently received high-dose therapy with either cyclophosphamide and total body irradiation or busulfan and cyclophosphamide. An additional dose of rituximab was administered to the patients 7 days after hematopoietic reconstitution. Mobilization of an adequate number of cells was achieved in 23 of the 25 patients with a median 1.07×10^7 CD34 cells/kg. When tested by a sensitive PCR assay, stem cell products in 6 of 7 patients were found to be free of tumor contamination. With the exception of transient neutropenia that occurred in 25% of patients approximately 100 days posttransplant, no significant increase in toxicity

Table 1. — Blood and Marrow Transplantation Plus Rituximab

Author	Regimen	Disease	No. of Patients	PCR Conversion From Positive Baseline
Buckstein et al ¹¹	Rituximab/high-dose chemotherapy followed by ASCT and 2 additional 4-week courses of rituximab posttransplant	Low/indolent NHL or MCL	14	7 of 7 pts
Flinn et al ¹²	Rituximab/high-dose chemotherapy followed by ASCT and 1 additional rituximab dose posttransplant	Low/indolent NHL or MCL	25	6 of 7 pts
Magni et al ¹³	High-dose chemotherapy/rituximab (3 cycles) followed by ASCT	Low/indolent NHL or MCL	15	14 of 15 pts
Flinn et al ¹⁴	Rituximab/high-dose chemotherapy volleyed by CD34-positive selection and ASCT, and 4 additional rituximab doses posttransplant	Low/indolent NHL or MCL	65	13 of 14 pts (10 of 14 pre-CD34-positive selection)
Voso et al ¹⁵	CHOP followed by rituximab and high-dose cytosine arabinoside/mitoxantrone stem cell mobilization	Low/indolent NHL or MCL	18	7 of 7 pts
Horwitz et al ¹⁶	ASCT followed by adjuvant rituximab (2 doses 6 months apart)	Low/indolent NHL	20	—

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone
ASCT = autologous stem cell transplantation
NHL = non-Hodgkin's lymphoma
MCL = mantle cell lymphoma

was noted with the addition of this therapy when compared to standard transplant regimens. This neutropenia was transitory and resolved spontaneously or with filgrastim and was not associated with significant infections except in 1 patient who developed progressive pancytopenia and died on day 232 of multisystem organ failure. This same group¹⁴ presented data from 65 patients with indolent lymphoma who underwent the same regimen previously described, except that patients received 4 doses of rituximab posttransplantation. Following mobilization, 51 patients underwent an additional ex vivo purging with positive CD34 selection. With a median follow-up of 195 days, the event-free survival was 82.8% at both 1 and 2 years. Of note, assessment of tumor cell contamination in the peripheral stem cell graft before and after CD34 selection was done by lymphoma colony formation assay and by PCR detection of the Bcl-2 mutation. Eleven of 55 in vivo purged grafts and 3 of 51 CD34 positively selected grafts grew lymphoma colonies. PCR analysis showed the absence of the t(14;18) translocation in 10 of 14 in vivo purged grafts and in 13 of 14 grafts following positive purging with CD34 selection.

In a small study, Voso et al¹⁵ treated 18 patients with follicular lymphoma and mantle cell lymphoma with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy followed by mobilization with rituximab and high-dose cytarabine arabinoside (Ara-C) and mitoxantrone. They reported the disappearance of the t(14;18) translocation in the grafts of all 7 patients tested. Long-term outcome was not reported.

An important aspect of the use of MAbs in the transplant setting is when to incorporate them during the transplant procedure. Results from various trials, including the pivotal trial that led to the approval of rituximab in the United States, clearly indicate that this antibody is efficacious in patients who relapse with a follicular lymphoma after ASCT. It is conceivable that when used as an adjuvant treatment, MAb may increase the efficacy of the transplant preparative regimen by destroying any neoplastic cells that remain after the high-dose therapy.

Horwitz et al¹⁶ reported minimal toxicity in their experience using rituximab as adjuvant therapy in the posttransplant setting. Forty days after infusion of their autologous stem cell grafts, 20 patients with B-cell NHL received 4 weekly infusions of 375 mg/m² of rituximab. In addition, 6 months after transplantation, patients also received a second course of rituximab. Rituximab infusion was well tolerated with minimal toxicities in all of the patients. Between 60–210 days post transplant, 13 episodes of grade 3–4 neutropenia was experienced in

9 of 20 patients. The episodes of neutropenia resolved except for one episode of febrile neutropenia and one episode of varicella zoster virus infection as the only clinically significant complications. Long-term outcomes have not yet been reached. Similar to the above reported study,¹⁴ administration of 4 doses of rituximab 375 mg/m² was associated with late adverse events and included 3 deaths (at day 125, 190, and 325), neutropenia, disseminated herpes zoster, and atypical mycobacterial infection. These preliminary studies suggest that the addition of rituximab to autologous blood transplantation in the adjuvant setting is feasible. However, there may be an increase in complications including cytopenia and infections.

Overall, these studies indicated not only the feasibility of using MAb in combination with high-dose chemotherapy and autologous stem cell rescue, but also the possible responses and outcomes these strategies may generate for patients with NHL.

Radioconjugated MAb

The prospect of using MAbs conjugated to radionuclide to deliver targeted radiation therapy has been gaining clinical interest. Radioimmunotherapy (RIT) takes advantage of the radiation sensitivity of hematologic malignancies and of the fact that antigen internalization is not required to mediate cytotoxicity.¹⁸ RIT does not need to rely on complement fixation or activation of ADCC to produce an antitumor effect. Depending on the isotope, these agents emit radiation that can have an effect on 1 to 5 mm or more and thus do not have to reach every malignant cell to remain effective.¹⁹ Despite the use of mouse rather than human antibodies, immunogenicity is less a problematic issue as such antibody preparations generally are given only once. However, RIT may cause myelosuppression that varies depending on dosing, bone marrow reserve, and marrow involvement with cancerous cells. In addition, therapy with these agents may be associated with long-term toxicity such as the apparition of secondary malignancies including myelodysplastic syndromes and leukemia.²⁰

Several agents for RIT are available that have been shown to have significant anti-lymphoma activity. Some of these have been tested in clinical trials in myeloablative doses in combination with autologous stem cell support or ABMT (Table 2). The feasibility of this concept was demonstrated in a phase I study by Press et al²¹ in which 19 patients were treated with escalating myeloablative doses of the ¹³¹I-labeled B1 antibody in combination with ASCT. The maximum tolerated dose (MTD) was found to be 27.25 Gy, with the most com-

Table 2. — Blood and Marrow Transplantation With Radioimmunotherapy

Radiolabeled	Disease	Regimen	No. of Evaluable Patients	Response Reported
¹³¹ I-B1 ²¹	Refractory low/intermediate NHL	RIT followed by ASCT	19	16 CR (100% RR)
¹³¹ I-B1 ²²	Refractory low NHL	RIT followed by ASCT	21	16 CR (86% RR)
¹³¹ I-B1 ²³	Refractory low/intermediate NHL	RIT + etoposide/cyclophosphamide followed by ASCT or ABMT	31	24 CR (87% RR)
¹³¹ I-B1 ²⁴	Refractory low/intermediate NHL	RIT followed by ASCT/ABMT	23	12 CR
⁹⁰ Y-ferritin ²⁵	Poor prognosis Hodgkin's lymphoma	RIT followed by ABMT	29	9 CR (62% RR)
⁹⁰ Y-ferritin ²⁷	Poor prognosis Hodgkin's lymphoma	RIT + cyclophosphamide/ carmustine/etoposide followed by ABMT	12	3 CR

NHL = non-Hodgkin's lymphoma
RIT = radioimmunotherapy
ABMT = autologous bone marrow transplantation
ASCT = autologous stem cell transplantation
CR = complete response
RR = response rate

mon dose-limiting toxicity being on the lungs. A complete remission was observed in 16 patients, a partial response in 2 patients, and a minor response in 1 patient. Sixteen of the 19 patients were alive after a median follow-up of more than 26 months, with 10 patients having relapsed after remissions lasting 2 to 18 months. In subsequent phase II studies,²² these investigators confirmed the MTD of 27 Gy for anti-B1 ¹³¹I antibody. Complete remission was achieved in 16 of 21 patients, 2 patients had a partial remission, and 1 achieved a minor response.

The single agent anti-B1 ¹³¹I antibody, when given in myeloablative doses, appears promising. However, many patients have relapsed from this therapy. In an attempt to improve on their previously obtained results, Press and colleagues²³ completed a phase I-II study in which 52 patients with relapsed NHL were treated with a combination of a myeloablative dose of anti-B1 ¹³¹I RIT, etoposide, cyclophosphamide, and ABMT or ASCT. Patients received a therapeutic infusion of anti-B1 ¹³¹I antibody. The amount of ¹³¹I varied according to dose level and was calculated based on the amount of radiation delivered to a critical organ such as the liver or lungs. Patients subsequently received dose-level-specific doses of cyclophosphamide and etoposide. The MTD of anti-B1 ¹³¹I was 25 Gy, when used in combination with 60 mg/kg of etoposide and 100 mg/kg of cyclophosphamide. Remarkably, in comparison to its use as a single agent, the MTD of anti-B1 ¹³¹I was not that much lower when used in combination. Of the 52 patients treated, 3 died and 8 had nonmeasurable dis-

ease after mobilization. Of the 31 evaluable patients, 24 had a complete response, 3 had a partial response, and 2 had stable disease. Of the 49 patients who received the entire regimen, 42 had a complete response. An overall survival rate of 83% and a progression-free survival rate of 68% were seen after a median follow-up of 2 years. This therapeutic approach compared well with a nonrandomized control group of patients treated at the same institution who received the same drug dosages but 120 Gy total body radiation instead of the MAb. The overall and progression-free survival rates were 53% and 36%, respectively.

Vose and colleagues²⁴ have reported preliminary results from a dose-finding study of BCNU (carmustine), etoposide, Ara-C, and melphalan (BEAM) and anti-B1 ¹³¹I in 23 patients with CD20+ NHL. Successive cohorts of patients received increasing doses of radiation (30 to 75 Gy) based on whole-body dosimetry followed by ABMT. All patients had a hematologic recovery by day 12. There were no treatment-associated deaths. At the time of the last analysis, 57% of the patients had a complete remission and 9% had a partial response, for an overall response rate of 66%. With a median follow-up time of 12 months, the estimate 1-year event-free survival rate was 60% and the estimated overall survival rate was 78%.

Alternatives to ¹³¹I-labeled antibody are ⁹⁰Y or ¹⁸⁶Re-labeled antibodies. It remains unclear which radioisotope and what dose schedule will prove to be more effective for the treatment of NHL. Phase I-II studies

Table 3. — Rationale for In Vivo Purging

No cross-resistance with chemotherapy
Is safe
Works as chemosensitizer
May be used as adjuvant therapy
Targets neoplastic cells
No effect on stem cell function and engraftment
Significant purging potential as demonstrated by polymerase chain reaction
Can be used in combination with chemotherapy or other immunotherapy agent, including MABs

have been conducted with a variety of schedules and doses of ^{90}Y -labeled antiferritin and autologous bone marrow rescue in patients with refractory Hodgkin's disease. Patients in a study by Vriesendorp et al²⁵ received doses ranging from 50 mCi in a single dose to a total of 80 mCi administered in 2 doses of 40 mCi each. The MTD was never reached. While all patients received autologous marrow support, it is not clear that the regimen was truly myeloablative. Winter et al²⁶ reported their experience from a dose-finding study in which patients with relapsed or refractory CD20-positive NHL were treated with escalating doses of ^{90}Y in combination with standard high-dose BEAM chemotherapy and autologous peripheral blood progenitor cells transplantation. Doses of 10 Gy, 30 Gy, or 50 Gy were given in groups of 3 to 6 patients on day 14. Median time to engraftment was 10 days for 1,000 granulocytes and 20 days for platelets. A decline in dose-limiting toxicity in diffusion capacity for carbon monoxide (DLCO) was documented in 2 of the 3 patients who received the 50 Gy dose. In terms of complication such as nausea, vomiting, stomatitis, diarrhea, hemorrhage, and infection, toxicity was equivalent to that of what is usually seen with standard high-dose BEAM chemotherapy alone. Another feasibility study²⁷ has been conducted with ^{90}Y -labeled antiferritin and cyclophosphamide, carmustine, and etoposide in 12 patients with refractory Hodgkin's disease. Patients received between 18 and 33 mCi. Four of the 12 patients died early of transplant-related causes, and 3 remained in remission for greater than 2 years.

Conclusions

Enormous advances have been achieved in the past 25 years toward safe and effective MAb-based targeted immunotherapy. Various antibodies are now available or are in the process of being approved for the treatment of lymphoid malignancies. Because of their activity, favorable toxicity profile, convenient dose scheduling, and lack of cross-resistance with chemotherapy, MABs have become an important modality to be used in conjunction with other therapies (Table 3). Several trials have shown MABs to have significant activity when used as single agents, in combination with chemotherapy, and in conjunction with autologous stem cell transplantation. When used in conjunction with autologous stem cell transplantation, unconjugated and radiolabeled antibodies appear to be promising tools for the eradication of lymphomatous cells in heavily pretreated or chemotherapy-refractory B-cell NHL. However, a definite role for these antibodies is yet to be determined before they can be considered part of the routine care of patients. Some of these considerations include how to integrate

naked and radiolabeled antibodies, the choice of isotope, the choice of antibody or antibodies, and the timing of the administration of the antibody.

Although randomized clinical trials are lacking, a review of previous clinical trials suggests that in vivo therapeutic strategies may be superior to in vitro strategies in terms of overall success rate in harvesting uncontaminated stem cells that are fully able to engraft, even after exposure to myeloablative regimens. Explanation for this observation may lie in the excellent bioavailability of MABs, therapeutic contribution from the host immune system, and synergism with high-dose chemotherapy. Overall, immunotherapy and especially RIT, when given with chemotherapy, appear to work more effectively than the single modality. Data from early in vitro purging studies indicate that combinations of antibodies appear superior to single antibody.⁷ This finding may hold true for in vivo purging or even posttransplant immunotherapy. In addition, in vivo purging is a more convenient strategy compare with in vitro purging that requires additional manipulation.

The addition of MAB-targeted therapy to high-dose therapy is an exciting strategy that may have a significant impact on patients undergoing these treatments. Follow-up is needed to assess the long-term risk of developing infection or secondary malignancies. An improvement in survival needs to be demonstrated in randomized clinical trial before these regimens can be considered part of the standard of care for the treatment of NHL.

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