**Immunotherapy in conjunction with autologous and allogeneic blood or marrow transplantation in lymphoma**

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**Summary**

Relapse is the major obstacle for successful transplantations in lymphoma. One of the ways to reduce relapse rates is to intensify immune-mediated effector mechanisms. Graft-versus-lymphoma may be achieved either by administration of cytokines or by allogeneic cell-mediated adoptive immunotherapy. The use of allogeneic non-myeloablative stem cell transplantation (SCT) is another option which may be applicable to all age groups. It remains to be seen whether non-myeloablative SCT will result in a lesser degree of relapse and higher disease-free survival in lymphoma patients.

**Key words:** graft-versus-lymphoma, immunotherapy, interferon-α, interleukin-2, minimal residual disease

**Introduction**

Although both Hodgkin's (HD) and non-Hodgkin's lymphoma (NHL) are responsive to conventional doses of chemotherapy, in a substantial proportion of the patients, particularly with NHL, relapse cannot be avoided. Patients with primary resistant disease or with relapse following front-line remission induction protocols due to residual tumor cells escaping chemoradiotherapy or with tumor cells acquiring resistance to subsequent doses of chemotherapy are unlikely to be cured unless they respond to high, myeloablative doses of chemoradiotherapy supported by autologous blood or marrow stem cell transplantation (autoBMT) [1]. However, the relapse rate following autoBMT using maximal tolerated doses of chemoradiotherapy is still very high due to minimal residual disease (MRD) which cannot be eliminated with any of the available modalities [2].

In view of the above, introducing another modality at the stage of MRD, when additional chemotherapy is unlikely to be beneficial except causing additional procedure related toxicity seems most rational. It has been shown that in patients with acute and chronic leukemia, tumor eradication following myeloablative doses of chemoradiotherapy supported by autologous blood or marrow stem cell transplantation (autoBMT) [1] is achieved. However, the relapse rate following autoBMT using maximal tolerated doses of chemoradiotherapy is still very high due to minimal residual disease (MRD) which cannot be eliminated with any of the available modalities [2].

In view of the above, introducing another modality at the stage of MRD, when additional chemotherapy is unlikely to be beneficial except causing additional procedure related toxicity seems most rational. It has been shown that in patients with acute and chronic leukemia, tumor eradication following myeloablative doses of chemoradiotherapy supported by autologous blood or marrow stem cell transplantation (autoBMT) [1] is achieved. However, the relapse rate following autoBMT using maximal tolerated doses of chemoradiotherapy is still very high due to minimal residual disease (MRD) which cannot be eliminated with any of the available modalities [2].

**Cytokine mediated immunotherapy (CMI)**

A variety of recombinant cytokines may potentially be used to prevent or treat relapse following autoBMT. Some of these cytokines may cause direct antitumor effects, while others may facilitate immunological recognition or activate anti-tumor effector mechanisms following autoBMT. Immune suppression, including depressed absolute number of CD4+ T cells, decreased T-cell response to mitogens, antigens or allogeneic stimulation, and profound impairment of interleukin-2 (IL-2) production, has been observed for up to one year following autoBMT, hence, it seems important to restore the immunocompetence of the recipient that may be impaired by high-dose chemotherapy required to reduce the tumor load [13].
In order to investigate the possible use of cytokines for eradication of MRD following autoBMT we have used a murine model of B-cell lymphoma (bcl-1) [14, 15]. We have demonstrated that administration of high-dose recombinant human IL-2 (rIL-2) following syngeneic BMT in BALB/c mice resulted in complete cure of mice inoculated with a small but not large tumor inoculum [15]. Only high doses of rIL-2 (three daily doses of 600,000 IU intraperitoneally for five days) were effective whereas the use of lower doses of rIL-2 (6,000 IU twice daily) resulted in enhancement of tumor progression. Tumor dormancy. Intermediate doses of rIL-2 (three daily doses of 60,000–300,000 IU intraperitoneally for five days) proved ineffective at all [14]. Following syngeneic BMT high dose rIL-2 given for five consecutive days was initiated on day +1, +7, or +21 following BMT [16]. Mice receiving no rIL-2 therapy relapsed and died within 50 days following BMT, whereas mice receiving high dose rIL-2 showed long term disease free survival. The optimal time for rIL-2 initiation was determined to be three weeks after BMT, with 90% of the mice surviving with no evidence of disease for more than one year. Kinetics of lymphocyte reconstitution following syngeneic BMT indicated a steep increase in the absolute number of peripheral blood lymphocytes (PBL) on days +17 through +24.

It is conceivable that maximal efficacy of rIL-2 therapy was elicited when rIL-2 was administered at the time of peak regeneration of lymphocytes because lymphocytes, rather than tumor cells, appear to be target cells for rIL-2. Similarly, when 10^6 bcl-1 cells were given one day after syngeneic BMT to simulate quantitative MRD following autoBMT, rIL-2 therapy given at 14 days after BMT seemed effective in prolonging disease free survival, in contrast to the same regimen given one day after BMT [16]. The anti-tumor effects induced by high-dose rIL-2 could be further amplified by co-administration of IFN-α which resulted in enhancement of the ability to resist a larger inoculum of bcl-1 even when lower doses of rIL-2 were used, which by themselves were ineffective against bcl-1 (unpublished data).

IL-2, a second class hormone, is a 15–17 kDa glycoprotein that is produced mainly by activated CD4 cells, usually as a result of stimulation by an antigen presented by a macrophage [17]. RIL-2 acts by binding to the specific IL-2 receptor (IL-2R), composed of non-covalently associated p55 and p75 subunits, expressed on T, B, and NK cells, and has a central role in the proliferation and differentiation of these cells [18, 19]. The clinical use of rIL-2 was initiated by Rosenberg et al. [20] with beneficial effects, though with infrequent incidence of cure, observed especially but not exclusively in patients with advanced metastatic renal cell carcinoma and malignant melanoma.

RIL-2 has also been shown to activate cytotoxic cells against lymphoma cells in vitro [21, 22]. In pilot clinical trials antitumor effects were also observed in patients with NHL and HD [23–28] including encouraging preliminary results in 20%–25% of previously heavily treated patients, including some complete remissions over a follow-up period of up to 26 months [23–28].

Several groups have recently reported their experience with rIL-2 for lymphoma patients undergoing autoBMT. Fefer et al. [29] reported on phase II clinical trials which aimed to determine the toxicity and efficacy of rIL-2 administered early after autoBMT for human hematologic malignancies. Sixteen patients with malignant lymphoma (12 NHL, four HD) received rIL-2 plus autologous lymphokine activated killer (LAK) cells [29, 30]. At the time of autoBMT, seven patients were in first relapse, and nine in second relapse. The treatment consisted of rIL-2 given within a median of 31 days after autoBMT. Eight patients were still in complete remission (CR) 15–31 months (median 20 months) following autoBMT. Seven patients relapsed five to 19 months (median eight months) after autoBMT and one died of infection while still in CR 14 months following autoBMT [29, 30].

α-interferon is a cytokine that has been shown to have an anti-proliferative effect in patients with CML and hairy cell leukemia [31, 32]. Interferons have been shown to augment NK activity both in experimental animals and humans [33, 34]. Furthermore, combination therapies of rIL-2 and α-interferon have been shown to function synergistically in augmenting cytolytic activity in mice, both in vitro and in vivo [35, 36]. Both rIL-2 and α-interferon were able to augment the suppressed NK cytolytic activity of lymphocytes isolated from CML patients [37, 38]. In vitro, the combination of both cytokines had a synergistic effect and potentiated NK mediated cytotoxicity [38]. Moreover, the synergistic effect of α-interferon and rIL-2 has recently been demonstrated in patients with solid tumors and advanced metastatic cancer [39–42]. α-interferon may be able to enhance the expression of specific antigens on target cells, which may make them more susceptible to cytotoxic cells activated and expanded by rIL-2. α-interferon has been used in pilot clinical trials in lymphoma patients either alone or in conjunction with chemotherapy [43–46]. It has been shown to be effective in evoking antitumor response in 40%–50% of the patients studied with low-grade NHL, including complete response in 5%–10% of these patients [43–45]. The results of α-interferon given together with chemotherapy have proven significantly better than chemotherapy alone [46]. On the basis of the above information, we recently initiated a pilot clinical trial utilizing α-interferon and IL-2, given either sequentially or concomitantly in patients with hematological malignancies, focusing on the treatment at a stage of minimal residual disease in patients with lymphoma with very encouraging results [47]. Our approach was aimed at achieving a synergistic effect between the cytokines, utilizing lower, hence safer, doses of rIL-2 and α-interferon given in an outpatient setting over a longer period of time rather than following the commonly used approach utilizing high doses given by bolus injections or continuous infusion during hospitalization.

In view of the above, and in order to reduce relapse rates following autoBMT by induction of lymphokine
mediated anti-tumor effect, we recently conducted a phase IIb clinical trial on 56 malignant lymphoma (ML) patients with MRD post autoBMT utilizing a combination of rIL-2 and IFN-α subcutaneously (s.c.) in an outpatient setting, and compared the results to 61 matched historical controls [10]. Fifty-six patients (38 men, 20 women) aged 10–53 (median age 35) years, were enrolled in the study. Thirty-two patients had NHL and 24 patients had HD. Sixty-one ML patients (NHL 36, HD 25) served as historical controls. Disease stage, sex and age were statistically similar in the study group and the historical controls: 44 patients (79%) in the study group and 43 patients (70%) in the historical controls were stage III–IV at diagnosis, while 12 patients (21%) in the study group and 18 patients (30%) in the historical controls were stage I–II. Thirty-three patients (58%) in the study group and 37 patients (60%) in the historical control group had B symptoms. The frequency of NHL high-grade histology was 36% in the controls in comparison with 22% in the study group. Most of the patients in the study group and historical controls were transplanted in an advanced stage of disease, as 63% of the study group patients and 69% of the historical controls were transplanted after first relapse or more. Conditioning regimen (TECAM) included thiopeta (40 mg/m² × four days), etoposide (200 mg/m² × four days), cytosar (200 mg/m² × four days), cyclophosphamide (60 mg/kg × one day), and melphalan (60 mg/m² × two days). There was no difference in the conditioning regimen between the immunotherapy treated patients and the historical control group. The median time interval between autoBMT and cell mediated immunotherapy (CMI) was fixed at four (2.5–10) months, in view of the need for adequate hematopoietic reconstitution before the initiation of cytokine administration. After stabilization of peripheral blood counts (white blood cells >2.5 × 10⁹/l and platelets >75 × 10⁹/l), patients were treated with daily s.c. injections of Chiron rIL-2 (Proleukin) (3–6 × 10⁶ international units (IU)/m²/d), combined with α-interferon (Roferon A; Hoffman La Roche, Switzerland) 3 × 10⁶ U/d, for five consecutive days each week for four weeks, followed by a months break, and then a second identical course [10].

The overall survival of ML patients who received immunotherapy was significantly higher than that of NL patients who did not. Survival at 48 months was 90% (95% confidence interval (95% CI): 70%–97%) for the immunotherapy patients, and 46% (95% CI: 30%–60%) for the historical controls (P < 0.01). Similarly, the overall survival was significantly higher for the HD and NHL patients who received immunotherapy when compared to the historical controls. The survival rates at 48 months were 100% and 80% (95% CI: 43%–95% versus 57% (95% CI: 31%–76%) and 42% (95% CI: 24%–58%), respectively (P < 0.02).

The overall disease free survival (DFS) of ML patients who received immunotherapy was significantly higher than that of comparable ML patients in the historical control group who did not receive immuno-therapy. The actuarial DFS at 48 months was 70% (95% CI: 50%–84%) and 48% (95% CI: 32%–61%), respectively (P < 0.01). Similarly, the actuarial DFS was significantly higher for the NHL and HD patients after immunotherapy than for the historical controls. The actuarial DFS for NHL patients receiving immunotherapy at 48 months was 64% (95% CI: 36%–80%) and 41% (95% CI: 25%–48%) for patients who did not receive immunotherapy (P < 0.01). The actuarial DFS for patients with HD receiving immunotherapy at 48 months was 88% (95% CI: 50%–96%) and 60% (95% CI: 34%–78%) for patients who did not receive immunotherapy (P < 0.042).

The relapse rate was significantly lower for ML patients who received immunotherapy than for a similar cohort of patients belonging to the historical controls. Of the 56 patients who received immunotherapy, 11 (20%) relapsed (eight NHL and three HD patients), while of the 61 patients who did not receive immunotherapy 29 (46%) relapsed (21 NHL and eight HD patients) (P < 0.01).

All patients were evaluated for treatment related adverse events. Most of the toxic effects improved gradually with therapy and were manageable with standard antipyretic and analgesic agents. Most of the patients continued their regular activities while receiving treatment. WHO grade II–III fever, chills, and fatigue were very common and occurred in 86% of the patients. The intensity of fever, chills, and fatigue tended to decrease throughout the treatment course (fewer patients experienced these side effects on the second cycle of therapy than on the first). Anorexia (46.5%), nausea with or without vomiting (77%), and diarrhea were common adverse events. A mild erythematous, pruritic maculopapular rash was observed in 34% of the patients. Three patients had grade II–III hair loss. Mild neurotoxicity, consisting of depression, insomnia, and nervousness was observed in 34% of the patients. Mild to moderate anemia (8%–11%) was observed in 50% of the patients, while mild to severe thrombocytopenia without bleeding tendency occurred in 80% of the patients. Only nine patients required red blood cell or platelet transfusions. Grade II–III liver enzyme elevation was observed in half of the patients. The s.c. administration of α-interferon and rIL-2 resulted in transient inflammation and local induration of the injection sites, which persisted for up to two weeks after treatment. Allergic manifestations, including contact dermatitis and bronchial asthma (one patient), were observed. One patient developed severe cardiotoxicity with cardiogenic shock responding to intravenous fluid and dopamine support. All side effects improved gradually and resolved after termination of the treatment. In only two cases did treatment have to be discontinued or interrupted because of toxicity.

We subsequently wanted to see whether modification of the immunotherapy schedule by reducing rIL-2 to one week (3–6 × 10⁶ IU/m²/d), followed by combined rIL-2/α-interferon for one month and extending α-interferon to 6 months (3 × 10⁶ U/d × 3/w) would improve efficacy.
and/or tolerability. Thirty-eight patients (25 men, 13 women), of median age 34 (18–57) years, were enrolled in the new immunotherapy protocol (pulse IL-2 followed by IFN-α maintenance immunotherapy). Twenty-four patients had NHL (high grade nine, intermediate nine, low six) and 14 HD (NS nine, MC four, LD one). Of the NHL patients 13 were transplanted in remission (CR² 11, CR¹ two), eight in partial remission and three with refractory disease. Of the HD patients seven were transplanted in remission (CR² six, CR¹ one), five in partial remission, and two with refractory disease. The conditioning regimen included thiotepa, etoposide, cyclophosphamide, cytosar, and melphalan. The immunotherapy protocol was initiated upon stable engraftment. Overall survival rate at 48 months was 83% (95% CI: 62%–93%), while actuarial DFS was 65% (95% CI: 42%–76%. Figure 1). For NHL patients the figures were 76% and 61% for survival and DFS, respectively, (Figure 2) while for HD patients the corresponding values were 91% and 71%, respectively (Figure 3). Toxicity, as was also seen in the previous cohort, was minimal and in no case did treatment have to be interrupted because of toxicity [48].

We are currently conducting a multicenter prospective randomized trial, investigating our newest rIL-2/α-interferon combination for intermediate and high-grade lymphoma and HD in an attempt to confirm the benefit of cytokine-mediated immunotherapy in the setting of minimal residual disease. Overall, our preliminary data in the murine model of human disease utilizing the bcl-1 and the cumulative clinical data suggest that CMI may provide a safe approach for eradication or control of minimal residual disease in conjunction with autoBMT.

**Allogeneic cell-mediated immunotherapy (alloCT)**

*Allogeneic T-lymphocytes as anti-tumor effector cells*

AlloBMT represents the most effective mode of therapy of resistant leukemias and lymphomas primarily due to the combination of maximal tolerated doses of chemoradiotherapy and immune-mediated GVL and GVLy effects induced by donor immunocompetent T cells present in the graft. The role of allogeneic cell-mediated immunotherapy (alloCT) in conjunction with alloBMT is best documented by comparing the rate of relapse of patients undergoing syngeneic and autoBMT with the rate in patients undergoing alloBMT, both being conditioned by identical chemotherapy [3, 49]. As was consistently shown, the relapse rate in acute and chronic leukemias is negatively correlated with acute and chronic GVHD [3, 49]. Experimental and clinical data on the negative role of cyclosporine A in GVL effects also supports the positive role of T cells in the GVL effects [50, 51]. All of the above suggest that T-lymphocyte-dependent immune effects play a major role in controlling MRD in conjunction with BMT. In view of these findings, it seemed reasonable to take advantage of the immune-mediated effector mechanisms that can be induced with immunocompetent donor lymphocyte infusion (DLI) to reverse relapse or better to reduce the risk of relapse following alloBMT. Indeed, we have shown that relapse following alloBMT may be successfully reversed resulting in cure following DLI in patients with a large variety of hematologic malignancies [52–56]. Although CML is the disease that responds best to DLI following alloBMT, many patients with lymphoid malignancies responded as well [53], including the first patient with pre-B ALL with bulky extramedullary disease [55], best response rates were observed in patients with CML [54, 56].

**Amplification of anti-tumor potential of allogeneic lymphocytes with rIL-2 in vivo and in vitro**

As will be shown below, we have hypothesised that T lymphocytes mediating GVL effects could be cytokine-
activated in vivo and/or in vitro with rIL-2 in experimental animals and man. Using the bcl-1 model of murine lymphoid leukemia/lymphoma [14, 15] we have shown long ago that GVL effects can be induced by alloBMT independently of clinical overt GVHD following nonmyeloablative conditioning [57]. GVL was induced and maintained by donor T lymphocytes, predominantly CD8+ cells [58]. GVL effects could be induced with allogeneic donor lymphocytes (C57BL/6) inoculated into MHC incompatible BALB/c recipients although donor cells were tolerant of host alloantigens [59, 60]. The efficacy of GVL effects were amplified substantially with rIL-2 administration in vivo both in tolerant chimeras [59] and following administration of alloreactive donor spleen lymphocytes [50, 61].

We have previously documented that following induction of chimerism recipients develop resistance to increments of donor's immunocompetent T cells and if given at sufficiently long time interval from BMT, GVHD could no longer be induced even in chimeras made across MHC [62]. Thus instead of risking the recipient with GVHD while attempting to induce GVL during the immediate post transplant period, GVL can be induced much safer late following induction of chimerism [62, 63]. Our observation was recently confirmed using another model of murine leukemia [64]. Based on the aforementioned two principles, we hypothesized that optimal and relatively safe GVL effects may be induced by gradual increments of immunocompetent donor lymphocytes given after induction of bilateral transplantation tolerance by alloBMT with further possible potentiation of GVL effects with concomitant administration of a short course of low-dose rIL-2 in vivo [55, 63].

Our data suggest that both immunocompetent allogeneic lymphocytes and rIL-2 can play an important role in treatment and prevention of relapse, especially when alloCT is applied as early as possible at the stage of MRD. The combination of both allogeneic cells and rIL-2 seemed synergistic and much more effective than any of the agents used alone, particularly when the
tumor load increases. We believe that in addition to unfavourable effector-target ratio, large tumor bulks tend to tolerize host reactive donor T cells. Interestingly, we have preliminary data to suggest that alloCT may be occasionally effective at the stage of MRD even following autoBMT [65, 66]. Based on the cumulative clinical experience and the large number of patients successfully treated for the past 11 years in different centers, all confirming the therapeutic potential of alloCT induced with DLI following alloBMT, there seems to be no question that this mode of biologic therapy may revive the interest in immunotherapy as a modality for treatment of otherwise incurable diseases.

Allogeneic non-myeloablative stem cell transplantation as a future method for combining stem cell transplantation and adoptive allogeneic cell therapy

Myeloablative combinations of high-dose chemoradiotherapy followed by rescue with autologous or allogeneic blood or marrow-derived stem cell transplantation are common modalities to treat lymphoma and various hematologic malignancies resistant to conventional doses of chemotherapy. For patients with lymphoma as well as additional blood malignancies, the transplant procedure is considered mostly as a rescue procedure following myeloablative treatment in order to eradicate the basic malignancy by the cytoreductive agents given prior to autoBMT or alloBMT. Attempts to improve the disease-free survival by increasing the intensity of the conditioning regimen, have resulted in unacceptable toxicity. Considering the importance of GVL effects we have considered the possibility to eradicate tumor cells by adoptive allogeneic cell therapy following induction of a state of host-versus-graft tolerance rather than following myeloablative therapy as done in conventional alloBMT protocols [67-69]. The goal was to provide donor-derived T lymphocytes the opportunity to recognize and eradicate host-derived tumor cells while minimizing the duration of immunosuppressive treatment as anti-GVHD prophylaxis. This working hypothesis prompted us to develop a new approach to avoid the need for myeloablative conditioning which should no longer be regarded as an essential component of the alloBMT procedure. A similar approach using different components was also done in parallel by the MD Anderson group [70, 71].

Our preliminary data included 26 patients with standard indications for allogeneic BMT, including 13 patients with NHL fully resistant to all chemotherapy (two of them underwent secondary alloBMT for relapse [68, 69] 57-60 months post autoBMT). Conditioning prior to infusion of allogeneic stem cells included immunosuppressive treatment with six daily infusions of fludarabine (Fludara, Schering AG) 30 mg/m² (in adults the dose was adjusted to ideal body weight) for six consecutive days (days -10 to -5); oral busulfan 4 mg/kg/day for two consecutive days (days -6 to -5); and anti-T-lymphocyte globulin (ATG-Fresenius) 10 mg/kg/day for four consecutive days (days -4 to -1). G-CSF mobilized blood stem cell transplantation with standard dose of cyclosporin A as the sole anti-GVHD prophylaxis resulted in stable partial (n = 9) or complete (n = 17) chimerism. In nine patients absolute neutrophil count (ANC) did not decrease below 0.1 x 10^9/l whereas two patients never experienced ANC < 0.5 x 10^9/l. ANC > 0.5 x 10^9/l was accomplished within 10-32 (median 15) days. Platelet counts did not decrease below 20 x 10^9/l in four patients requiring no platelet support at all; overall platelet counts > 20 x 10^9/l were achieved within 0-35 (median 12) days. Fourteen patients experienced no GVHD at all; severe GVHD (grade 3-4) was the single major complication and the cause of death in four patients, occurring following early discontinuation of CS. Relapse was reversed by allogeneic cell therapy in two patients with lymphoid malignancies; one with resistant progressive NHL and the other with ALL [68]. The one patient with NHL, a male with bone and marrow infiltration who received an allograft from a sister is currently with no residual host DNA (male) by cytogenetic analysis and repeated PCR. Todate with an observation period extending over a year and a half the patient is disease free. Of the total of 26 patients treated with allogeneic non-myeloablative stem cell transplantation (alloNST) 81% are disease-free. The actuarial probability of disease-free survival at 14 months is 77.5% (95% CI: 53%-90%).

Successful eradication of malignant host hematopoietic cells by alloNST which can be followed with alloCT in case residual host cells need to be eradicated represents a potential new approach for safer and more rational treatment of a large variety of clinical syndromes with an indication for alloBMT. Transient mixed chimerism which in the long run may protect the host from severe acute GVHD may be successfully reversed post allogeneic BMT with graded increments of DLI, thus possibly resulting in cure while avoiding the use of lethal conditioning.

Conclusions

The use of allogeneic non-myeloablative stem cell transplantation, based on the potent immunosuppressive effects of the combination of fludarabine and Fresenius ATG, may help bypass frequent early toxicity and late complications which result from the combined effects of high-dose chemoradiotherapy in addition to prior conventional treatments, especially in the low and high age groups. In the low age group, in contrast to myeloablative allogeneic BMT, allogeneic non-myeloablative stem cell transplantation may reduce the incidence of growth retardation and infertility due to the unique sensitivity to chemoradiotherapy of the growth centers in the bones, the gonads and testicles. In elderly individuals, who normally may not be eligible for a standard alloBMT, allogeneic non-myeloablative stem cell transplantation...
may permit a relatively safe clinical application of a potentially curative procedure at all age groups, based primarily on adoptive immunotherapy rather than high-dose chemo-radiotherapy. It remains to be seen whether application of alloNST in patients with resistant NHL, a disease which affects many elderly individuals, can offer a better disease free survival over conventional autoBMT and alloBMT already shown to result in a lesser degree of relapse but little if any advantage in disease free survival due to transplant related complications.

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