



Review

Immunotherapy with Recombinant Human Interleukin 2 in Patients with Hematological Malignancies after Bone Marrow or Peripheral Blood Stem Cell Transplantation

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Abstract. High-dose chemotherapy in conjunction with bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) is increasingly being used for treatment of patients with hematological malignancies. Residual tumor cells, resistant to high-dose chemoradiotherapy, are responsible for recurrence of the disease. Interleukin 2 (IL-2), a pleiotropic cytokine which plays a central role in immune response, has been introduced in several clinical trials in patients with hematological malignancies after BMT or PBSCT to increase immunocompetence of these patients and eradicate residual malignant cells. At present there is no general agreement on the optimum dosage or route of administration and clinical trials also gave conflicting results. Establishment of optimum dosage schedules and methods of administration should enable a better assessment of the place of IL-2 in the treatment of these patients.

Key words: interleukin 2; bone marrow transplantation; peripheral blood stem cell transplantation.

High-dose chemotherapy in conjunction with bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) is increasingly being used for treatment of patients with hematological malignancies. Residual tumor cells, resistant to high-dose chemoradiotherapy, are responsible for recurrence of the disease. It is hypothesized that recombinant human interleukin 2 (rIL-2), administered early after transplantation, might eradicate residual tumor cells, thereby reducing relapse rate.

There is increasing evidence that the principal mechanism of cure after intensive chemotherapy is immune-mediated. This is evidenced by the observation of a reduced risk of leukemia relapse after allogeneic BMT when compared with autologous or syngeneic

BMT. Furthermore, an increased incidence of leukemic relapse has been reported after aggressive graft-versus-host disease (GVHD) prophylaxis with cyclosporin A² or T cell depletion²⁴.

Interleukin 2 is a cytokine capable of expanding cytotoxic T cells, enhancing cell activity, and activating lymphokine-activated killer (LAK) effectors^{15, 16, 25, 32, 34}. Laboratory studies have indicated that human leukemic blasts of both myeloid and lymphoid origin as well as lymphoma cells, may be lysed by LAK effectors^{6, 7, 18, 31}. Additionally, IL-2 may increase graft-versus-leukemia (GVL) effect after allogeneic BMT²⁴. It has been also shown that rIL-2, after autologous bone marrow transplantation, induces a syndrome consistent with GVHD^{8, 23} and therefore, might induce GVL effect.

Quantitatively, abnormal T cell parameters following BMT include a decreased absolute number of CD4⁺ T cells for as long as 2 years, a decreased response to mitogens, antigens and allogeneic cells in lymphoproliferative assays, and a profound impairment of IL-2 production^{17, 22, 39}, while retaining the ability to respond to exogenous rIL-2 administration^{21, 30}. Circulating IL-2-responsive cells, that can mediate LAK activity *in vitro*, are usually detectable as early as 2 weeks after autologous stem cell transplantation¹³.

Initial clinical trials have shown rIL-2 to be capable of inducing tumor regression in patients with metastatic solid tumors^{9, 35, 40}. IL-2 has been then introduced in several clinical trials in patients with hematological malignancies after BMT and PBSCT in several centers in both US and Europe (Table 1). These trials are representative for the bulk of published work to date. In all trials rIL-2 was started after BMT or PBSCT when patients had achieved stable hematopoietic recovery (neutrophils >0.5 G/l; and platelets >20.0 G/l). However, there are several problems inherent in interpreting results of clinical trials using rIL-2.

Recombinant human IL-2 has been used in various dosage regimens and protocols. At present there is no general agreement on the optimum dosage or route of administration. Patients tended to undergo a variety of treatments before receiving IL-2. Many studies included patients with different hematological malignancies^{4, 10, 19, 23, 26, 27, 29, 33, 38}. rIL-2 has been used alone^{1, 4, 11, 12, 19, 26, 27, 29, 33, 37, 38}, with LAK cells^{3, 23} or with IFN- α ^{10, 28} or IFN- γ ¹⁴. In some studies maximal tolerated dose was established at the beginning of the study^{3, 11, 33}. However, the relationship between dosage and response is unclear. In patients with solid tumors BUDD et al.⁵ did not find dose-dependent efficacy. There is only one prospective randomized multicenter trial¹ in adult acute lymphoblastic leukemia (ALL) comparing relapse rates of patients randomized to receive or not to receive IL-2 after autologous BMT published to date. Each group (receiving or not receiving immunotherapy) consisted of 30 patients. The 3-year post BMT probability of continuous complete remission was similar in both groups (29 vs. 27%, respectively). HAMON et al.¹¹ reported higher actuarial disease-free survival and lower actuarial risk of relapse in 7 acute myelogenous leukemia (AML) patients who received rIL-2 after autologous bone marrow transplantation (ABMT) in first remission as compared to 11 patients not receiving rIL-2. In patients, receiving rIL-2 within 21–58 months (median 32 months) from the time of ABMT, there was one relapse (actuarial risk 17%, 95% confidence intervals (CI) 3–31%); the disease-free survival was 71% (95%

CI 38–100%). In 11 patients with comparable remission induction and consolidation therapy not receiving immunotherapy with 24–45 months (median 29 months) follow-up the actuarial disease free survival was 36% (93% CI 8–64%), the actuarial relapse risk was 54% (95% CI 18–90%). KOŁECKI et al.¹⁴ used low dose IL-2 and IFN- γ as a maintenance treatment in children with high risk of acute leukemia and non-Hodgkin's lymphoma. There was no significant difference in disease-free survival in patients receiving or not receiving cytokines after ABMT. However, the median remission duration was increased in patients receiving immunotherapy as compared to that achieved in patients not receiving immunotherapy. NAGLER et al.²⁸ obtained encouraging results using rIL-2 and rIFN- α in lymphoma patients (32 patients with non-Hodgkin's lymphoma, 24 patients with Hodgkin's disease) after ABMT or PBSCT. The overall survival of malignant lymphoma patients who received immunotherapy was significantly higher than that of malignant lymphoma patients not receiving immunotherapy. The survival at 48 months was 90% (95% CI 70–97%) for immunotherapy patients and 46% (95% CI 30–60%) for historical controls ($p < 0.01$). Similarly, the overall survival was significantly higher in lymphoma patients as compared with the historical controls. Disease-free survival of malignant lymphoma patients, who received immunotherapy, was significantly higher than that of comparable malignant lymphoma patients in the historical control group who did not receive immunotherapy. The actuarial disease-free survival at 48 months was 70% (95% CI 50–84%) for immunotherapy patients and 48% (95% CI 32–61%), respectively ($p < 0.01$). Similarly, the actuarial disease-free survival was significantly higher for lymphoma patients after immunotherapy as compared with the historical controls ($p < 0.01$). The relapse rate was significantly lower for lymphoma patients who received immunotherapy in comparison to a similar cohort of patients belonging to the historical control. These preliminary results are encouraging and suggest that home-administered immunotherapy with rIFN- α and rIL-2 may intensify remission in malignant lymphoma patients with minimal residual disease following ABMT or PBSCT. The major difference is due to a decreased relapse risk: 17% (95% CI 3–31%) for IL-2 recipients compared with 54% (95% CI 18–90%) in the AML patients group not receiving IL-2.

Treatment related adverse events were not different from previously reported in patients with solid tumors receiving rIL-2 like nausea/vomiting, anorexia, loss of taste, hypotension, dizziness, toxicodermia, cardiac arrhythmia, fever, chills, fatigue, myalgia, contact der-

Table 1. Trials in patients with hematological malignancies receiving IL-2 with or without IFN- α , γ or LAK cells after BMT or PBSCT

Reference	No. of patients	Treatment regimen
ATTAL et al. ¹	30	total of 5 cycles every other week (first cycle 5 days, the following 4 cycles 2 days); at a dose 12×10^6 U/m ² /i.v.
BENYUNES et al. ³	8	$0.3\text{--}3.0 \times 10^6$ U/m ² /day for 5 days and after 6 days rest 0.3×10^6 U/m ² /day for 10 days
	5	3.0×10^6 U/m ² /day for 5 days, then leukapheresis for 3 days and received their LAK cells plus IL-2 (0.3×10^6 U/m ² /day for 10 days) i.v. infusion
BOSLY et al. ⁴	19	escalating dose from $3\text{--}30 \times 10^6$ U/m ² /day 5 day continuous i.v. infusion followed 6 days later by additional 4 1/2 day continuous infusion. This 15-day cycle was followed by a 15-day rest period followed by identical second cycle of treatment
GÓRSKI et al. ¹⁰	11	3×10^6 U IFN- α 3 times per week for 2–6 months; IL-2: 9×10^6 U/m ² /day for 4 days and after 8 days rest 4.5×10^6 U/m ² /day for 8 days
HAMON et al. ¹¹	7	IL-2 for 5 days by continuous i.v. infusion, initially as part of phase I/II trial; 195–480 μ g/day
HESLOP et al. ¹²	16	169–700 μ g/m ² /day for 3–5 day i.v. infusion
KOŁECKI et al. ¹⁴	22	repeatedly administered cycles of 4 weeks followed by 2–9 weeks intervals, one cycle consisted of IFN- γ 2.5×10^6 U/day/m ² , IL-2 1×10^5 U/day/m ² s.c. day 5; in the 2nd to 4th weeks IL-2 at the same dose day 1,3 and 5 sc.
LOPEZ-JIMENEZ et al. ¹⁹	13	4×10^5 continuous i.v. infusion for 3 months $8 \times 10^5\text{--}1 \times 10^6$ s.c. for 3 months
MASSUMOTO et al. ²³	14	9×10^6 U/m ² /day for 5 days i.v. followed by apheresis to provide cells for LAK generation. The cells were then cultured for 5 days with IL-2 (1000 U) and reinfused. A low maintenance course of IL-2 (0.3×10^6 U/m ² /day was administered for 10 days
MELONI et al. ²⁶	10	IL-2 i.v. for 5 days using a daily escalating protocol from 100 μ g/m ² /day to the maximum tolerated dose followed after 3 weeks by low-dose IL-2 for 5 days monthly
MESSINA et al. ²⁷	5	1×10^6 U/m ² /day for 6 days by i.v. infusion, a further 6 maintenance IL-2 cycles at 18×10^6 U/m ² /day on a monthly basis ($\times 6$)
	5	6×10^6 U/m ² /day, 1 $\times$ before bone marrow harvesting
NAGLER et al. ²⁸	56	IFN- α s.c. 3×10^6 U/days for 5 days/week combined with IL-2 s.c. $3\text{--}6$ U/m ² /day for 5 days/week for 4 weeks (2 cycles)
NEGRIER et al. ²⁹	20	18×10^6 U/m ² /day i.v. for 6 days
ROBINSON et al. ³³	15	escalating doses IL-2 $9\text{--}12 \times 10^6$ U/m ² /day for 4 days, after 4 days of rest, IL-2 1.6×10^6 U/m ² /day for 10 days
	52	previously determined maximum tolerated dose of induction IL-2, followed by the same maintenance IL-2 regimen
SALGADO et al. ³⁶	8	IL-2 s.c. 4 days/week from starting dose $0.5\text{--}2 \times 10^6$ U/m ² /day with weekly escalation of the dose ($0.5\text{--}1 \times 10^6$ U/m ²); maximum dose of administrated IL-2 was $2.5\text{--}6 \times 10^6$ U/m ² /day, planned duration of the treatment was 3–6 months
SIKORSKA-FIC et al. ³⁷	1	2.5×10^5 U/m ² /day IL-2 i.v. for 5 days, 5×10^5 U/m ² /day for 4 days, 5×10^5 U/m ² s.c. for 14 days, 7.5×10^5 U/m ² /day s.c. for 14 days
SOIFFER et al. ³⁸	10	2×10^5 U/m ² /day i.v. for 90 days

matitis at the injection site, moderate-severe headache, significant weight loss, inflammatory nodules at the injection site^{9, 11, 36}. Basic coagulation parameters and clinical biochemistry except for elevation of activity of liver enzymes in some studies did not change during therapy with IL-2. All side-effects diminished gradually and resolved after termination of treatment^{1, 3, 4, 10, 12, 14, 19, 23, 26-29, 33, 36-38}. Changes in hematological and immunological parameters during IL-2 treatment included: neutropenia³ thrombocytopenia^{3, 36} increase in eosinophil number¹⁹, lymphopenia followed by rebound lymphocytosis^{3, 4, 12}, increase of absolute number of CD16, CD56, CD8^{3, 4, 14, 27, 36}, CD25^{4, 37} increase in LAK activity^{26, 27}. Some authors reported induction of hemopoietic growth factors¹².

In conclusion, further randomized studies should

address the role of exogenous rIL-2 in the prolonged maintenance of complete remission and determine the group of patients in which rIL-2 is most likely to be effective. In addition, studies to date have grouped heterogeneous population together in order to evaluate the clinical and toxic effects of rIL-2. Further series should include classification of patients according to clinical and disease status in groups large enough for separate analyses in order to design regimens combining ablative chemotherapy and autologous marrow purging in tandem with administration of rIL-2, with or without LAK infusion or together with other immunomodulators. rIL-2 offers an adjunct to current therapy with the possibility of real therapeutic benefit but with firm evidence still required.

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