

ORIGINAL ARTICLE

Interferon- α after autologous stem cell transplantation in pediatric patients with advanced Hodgkin's lymphoma

D Petropoulos¹, LL Worth¹, CA Mullen^{1,2}, S Lockhart³, M Choroszy¹ and KW Chan^{1,4}

¹Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA; ³Children's Hospital of Austin, Austin, TX, USA and ⁴Texas Transplant Institute, San Antonio, TX, USA

Thirteen children with refractory or recurrent Hodgkin's lymphoma (HL) received high-dose chemotherapy and autologous hematopoietic stem cell transplant (ASCT). After hematologic recovery, 10 patients were given interferon- α (IFN- α) as adjuvant therapy, starting at a dose of 0.5×10^6 U/m² subcutaneously, three times a week. The dose was escalated as tolerated. Patients were treated for a median of 12 (4–24) months. Transient myelosuppression was the most common toxicity and led to temporary treatment interruption in five patients. The IFN- α dose was increased in nine patients, to a median final dose of 3.5×10^6 U/m²/week. With a median follow-up of 67 (range 25–114) months, nine of the 10 patients are alive and in continuous remission. One patient relapsed. Three patients were not treated with IFN- α initially, two because of rapidly progressive disease. One patient received IFN- α for treatment of relapse after transplant, and is alive in remission 10 years later. IFN- α has activity in children with advanced HL, and prolonged, low-dose treatment given after ASCT can be tolerated. Its therapeutic effect as a post-transplant adjuvant warrants further investigation.

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Introduction

Whereas the outcome of Hodgkin's lymphoma (HL) in children has improved over the past few decades, patients with relapsed or primary refractory disease continue to have a poor prognosis. A recent cooperative group study showed a 5-year event-free survival (EFS) in HL patients who relapsed after chemotherapy of 26%.¹ Patients with early disease progression had a particularly poor prognosis. Autologous hematopoietic stem cell transplantation

(ASCT) has been a commonly accepted retrieval strategy for adult HL patients. A case-controlled study suggested that the transplant outcome in children with HL was similar.² However, details of this treatment modality exclusively in pediatric patients are scarce. Among such reports, a 5-year overall survival (OS) was 43–95%, but the EFS was 31–62%.^{3–6} Most treatment failures were the result of relapse of the primary disease and patients with multiply relapsed HL fared poorly. Various strategies have been used to reduce the risk of tumor recurrence, without much success.^{7–11}

Interferon- α (IFN- α) is a biologic agent that has demonstrated activities in a number of malignancies. It produced objective responses and disease stabilization in patients with relapsed and refractory HL.^{12–14} These were usually noted after 3–4 months of IFN- α treatment.¹⁴ Although the response has been minor in the heavily pretreated patients, the efficacy of IFN- α might be better if the tumor burden was small. In a randomized trial, newly diagnosed HL patients given IFN- α after completion of chemotherapy had a better survival rate when compared to that of the controls.¹⁵ Given at a dose of $9–21 \times 10^6$ U/week, the toxicity was mainly myelosuppression.

The exact mechanism of action of IFN- α in HL is not clear. Its antiproliferative action is mediated through the activation of multiple signaling cascades involving different kinases.¹⁶ It modulates immune responses by amplifying T-lymphocyte activation and enhancing natural killer cell activity.¹⁷ Interferon also downregulates a number of proangiogenic growth factors.¹⁸ The regression of cavernous hemangioma in young children after prolonged, low-dose IFN therapy may be the result of this mode of action.¹⁹ We hypothesized that the administration of IFN- α after ASCT may be an effective adjunct and a gradual dose escalation regimen could be better tolerated. An extended duration of maintenance may be necessary. In this report, we describe our experience in a group of children with advanced HL.

Patients and materials

Patients

Between January 1994 and January 2004, 13 consecutive pediatric patients with advanced HL underwent ASCT in

Correspondence: Dr KW Chan, Texas Transplant Institute, 8201 Ewing Halsell, Suite 280, San Antonio, TX 78229, USA.
E-mail: kawah.chan@mhshealth.com
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our center. Patients were candidates if there was primary treatment failure, relapse within 12 months of initial diagnosis or multiple relapses proven by biopsy. Adequate organ functions were also required: left ventricular ejection fraction >50%, serum creatinine and bilirubin levels no more than twice the upper limit of normal for age, serum alanine aminotransferase level no more than three times the upper limit of normal and Lansky's performance status >70%. The transplantation protocols were approved by the institutional review board of The University of Texas MD Anderson Cancer Center, and written informed consent was obtained from parents or guardians for all patients.

Patients received a variety of salvage chemotherapy before ASCT. Radiation therapy to local disease was not routinely used. Disease status was assessed by CT and gallium scans after 2–3 cycles of treatment. In the last four patients, ^{18}F -fluoro-deoxyglucose positron emission tomography (FDG-PET) scans were also employed. Definition of disease status before hematopoietic stem cell transplantation (HSCT) was based on clinical evaluation and the aggregate of test results, although a negative FDG-PET scan was often accepted as indicative of complete remission. Depending on the prior history of chemotherapy exposure, up to two regimens might be given. After that, in the absence of rapidly progressive disease and/or organ dysfunction, patients were admitted for transplant. Chemo-responsiveness and residual disease were not used to determine transplant eligibility.

Conditioning regimens and stem cell transplantation

Over the 10-year period, several high-dose chemotherapy regimens were used. Seven patients received the BEAM regimen, consisting of carmustine $300\text{ mg/m}^2 \times 1$, etoposide $200\text{ mg/m}^2 \times 8$, cytarabine $200\text{ mg/m}^2 \times 8$ and melphalan $140\text{ mg/m}^2 \times 1$. Three patients were conditioned with CBV (cyclophosphamide $1500\text{ mg/m}^2 \times 4$, carmustine $300\text{ mg/m}^2 \times 1$ and etoposide $125\text{ mg/m}^2 \times 6$). Individual patients received the following regimen: busulfan (16 mg/kg) and cyclophosphamide (120 mg/kg); thiotepa (750 mg/m^2), busulfan (480 mg/m^2) and cyclophosphamide (120 mg/kg); and mitoxantrone (30 mg/m^2), thiotepa (750 mg/m^2) and etoposide ($125\text{ mg/m}^2 \times 6$). All but two patients received peripheral blood stem cells; both marrow graft recipients had failed prior stem cell mobilization attempts.

Post-transplant therapy

All patients underwent disease reassessment 4–6 weeks after ASCT. IFN- α therapy was started if there was no evidence of progressive disease, and when the blood counts were recovering (usually with an absolute neutrophil count (ANC) of more than $1.5 \times 10^9/\text{l}$ and a platelet count exceeding $75 \times 10^9/\text{l}$). The starting dose was $0.5 \times 10^6\text{ U/m}^2$ subcutaneously (s.c.) three times a week. If the ANC was stable and stayed above $3 \times 10^9/\text{l}$, and there were no other side effects, IFN- α was escalated by $0.5 \times 10^6\text{ U/m}^2/\text{dose}$. Some patients preferred to keep the same dose but to increase the frequency of injection to 5 days per week. The goal was to maintain an ANC above $1.5 \times 10^9/\text{l}$ and a platelet count of over $75 \times 10^9/\text{l}$. Treatment was planned for

12 months after transplant. Acetaminophen or ibuprofen $10\text{--}15\text{ mg/kg}$ was recommended before the injection and could be repeated, if necessary.

Follow-up after transplant

Patients were seen at least every 2 weeks while on IFN- α therapy. Complete blood counts and blood chemistry were carried out during each visit. Radiographic evaluation for HL was performed every 3 months during the first year, and every 6 months for two more years after transplant or when clinically indicated. Patients were also followed for thyroid, cardiac and pulmonary functions.

Statistical analysis

OS and EFS from the date of ASCT were estimated using the Kaplan–Meier method, using the Number Cruncher Statistical Software 2004 (NCSS, Kayville, UT, USA). The data were censored for analysis on 1 February 2006.

Results

Patients

The patient characteristics are shown in Table 1. Their median age was 15 (range 11–20) years. The duration of first remission was as follows: primary refractory ($n=2$), less than 12 months ($n=9$), more than 12 months ($n=2$). Both patients whose first remission lasted more than a year had multiple relapses. Seven of 13 patients had a history

Table 1 Patient characteristics

	N
Age (years)	11–20 (median 15)
Sex M:F	9:4
<i>Histology</i>	
Nodular sclerosing	10
Nodular sclerosing + ALCL	1
Lymphocyte predominant	2
<i>Disease status at ASCT</i>	
CR2/CR3	3/3
PR	2
SD/PD	5
<i>Prior chemotherapy regimens</i>	
2	5
3	5
4	3
<i>Prior radiation</i>	
Yes	12 ^a
No	1
<i>Source of stem cells</i>	
Peripheral blood cells	11
Marrow	2

Abbreviations: ALCL = anaplastic large-cell lymphoma; ASCT = autologous hematopoietic stem cell transplantation; CR = complete remission; PD = persistent or progressive disease; PR = partial remission; SD = stable disease.

^aTwo patients were irradiated more than once.

of extranodal disease and eight had 'B' symptoms. The patients had received a median of 3 (range 2–4) prior chemotherapy regimens. All but one also had radiotherapy; two were irradiated twice. Nine patients had chemosensitive disease at the time of ASCT, although one required two retrieval regimens before a response was seen. The median interval between diagnosis and ASCT was 16 months (range 6 months–9 years).

Autologous stem cell transplant

All patients survived high-dose chemotherapy. Recovery of ANC ($>0.5 \times 10^9/l$) and platelet ($>20 \times 10^9/l$) occurred after a median time of 10 (9–16) and 12 (11–31) days, respectively. Of the seven patients with demonstrable disease at the time of ASCT, the following response was observed: $>50\%$ tumor regression ($n=2$), minor (less than 50%) shrinkage ($n=3$), progressive disease ($n=2$). Two of the responders received further therapy in addition to IFN- α . One patient received 12 Gy of irradiation to residual mediastinal lymphadenopathy (dose limited by previous mantle irradiation) before starting IFN- α . Another was given an infusion of Epstein–Barr virus (EBV)-specific cytotoxic T cells several months into therapy.

Post-transplant IFN- α therapy (Table 2)

Ten patients began maintenance IFN- α at a median of 49 days post-transplant (range 33–127). The median duration of treatment of the entire group was 12 months, with seven patients treated for 11–14 months. Owing to miscommunication, one patient continued IFN- α for 24 months in his native country. One patient refused further IFN- α injections after 4 months of treatment. Treatment was stopped after 6 months in one patient when recurrent HL was detected. The dose of IFN- α was escalated in nine of the 10 patients. The median weekly dose of IFN- α at the end of treatment was 3.5×10^6 U/m² (range 2.0–6.5). In one patient, who returned to his native country 5 months after ASCT, the IFN- α dose was electively kept constant by his local oncologist.

Three patients did not receive IFN- α as maintenance. Two had primary refractory HL and had rapidly progressive disease after ASCT. Owing to administrative reasons,

the first patient of the series was not offered IFN- α after transplant. He relapsed in the lungs (biopsy proven) 18 months later and did not respond to chemotherapy. He was treated with IFN- α at a dose of 1×10^6 U/m² three times a week for 12 months. The patient remains alive and in continuous remission 9 years after completion of IFN- α .

Toxicity of IFN- α therapy

IFN- α was well tolerated. The most common toxicity was myelosuppression. This occurred during the first 2 months of IFN- α therapy. In five patients, treatment was withheld for 1–2 weeks to allow recovery. Blood counts became more stable with time and IFN- α dose escalation was possible in all patients (see above). Transfusion of red cells and platelet transfusion, and the administration of hematopoietic growth factor were not required for any patients during IFN- α therapy. Mild constitutional symptoms (fever, chills and headache) occurred in four patients, but none were severe enough to interfere with treatment. Most patients discontinued antipyretic premedication after 2–3 months. Two patients developed elevated thyroid stimulating hormone level while on IFN- α therapy. One patient required thyroid replacement therapy, whereas the test normalized in the other. Reversible peripheral neuropathy developed in one patient after 20 months of injections, as reported previously.²⁰

Follow-up

With a median follow-up of 61 (range 25–140) months, 10 of 13 patients (77%) are alive and in remission. Of the 10 patients who received IFN- α as adjuvant therapy post ASCT, nine (90%) are alive with no evidence of disease. They have been followed for 25–114 (median 67) months. Three patients died of HL: both untreated patients with rapidly progressive disease and one who relapsed after 6 months IFN- α . The cumulative probability of 5-year OS was 70% (95% confidence interval (CI) 40–100%) and the projected probability of 5-year EFS was 70% (95% CI 44–94%) for the whole group. There is no second cancer detected in any of the survivors.

Table 2 Clinical features of patients given IFN- α consolidation post ASCT

Patient no.	Pre-ASCT status	Post-ASCT status	Duration of IFN (months)	Max. IFN dose (10^6 U/m ² /week)	Follow-up (months)	Current status
1	PD	MR	24	3.1	114 ⁺	NED
2	PD	MR ^a	12	2.1	112 ⁺	NED
3	CR ₃	CCR	11	2.4	99 ⁺	NED
4	PR ₂	CR ^b	12	4.8	56 ⁺	NED
5	CR ₂	CCR	11	6.0	53 ⁺	NED
6	PR ₂	CR	6	3.9	6	Relapse, Died
7	CR ₂	CCR	12	6.5	42 ⁺	NED
8	CR ₃	CCR	14	4.5	31 ⁺	NED
9	CR ₃	CCR	6	2.0	29 ⁺	NED
10	CR ₂	CCR	12	2.4	29 ⁺	NED

Abbreviations: ASCT = autologous hematopoietic stem cell transplantation; CCR = continuous complete remission; CR = complete remission; IFN = interferon; MR = minor response; NED = no evidence of disease; PD = persistent/progressive disease; PR = partial remission.

^aPost ASCT radiation (see text).

^bCytotoxic T-cell infusion (see text).

Discussion

In this report, we showed that ASCT could be safely performed in children and adolescents with relapsed or refractory HL. IFN- α was well tolerated, even when started soon after transplant. The outcome in a small group of patients compares favorably with that in other reports.

In both adult and pediatric patients, recurrence of HL was the main cause of failure after ASCT.^{2-6,21} The relapse rate in several pediatric series ranged from 25 to 69%. Lieskovsky *et al.*⁴ noted that about half of the relapses occurred in previously uninvolved sites. Overall, the projected 5-year EFS after ASCT was only 31–62%.²⁻⁶

A number of strategies have been attempted to improve the treatment outcome. Augmentation of the preparative regimen (including tandem high-dose regimens), although feasible, did not improve transplant outcome.^{7,8} Local radiation therapy to sites of recurrent diseases has been reported to reduce the risk of further progression.⁹ However, most patients already had prior treatment and there is a limit to how much more irradiation could be tolerated. In addition, relapses may occur in previously uninvolved sites. Rapoport *et al.*¹⁰ administered four cycles of chemotherapy over a 1-year period in their transplanted patients. Owing to lack of compliance, less than half of the targeted patients actually received the planned treatment. Cytotoxic therapy post ASCT may be complicated by myelosuppression and opportunistic infections. The risk of second malignancies may also increase.

Cellular immunotherapy is a potential post-transplant therapy that could be well tolerated. Rooney *et al.*¹¹ infused EBV-specific cytotoxic T-lymphocytes as adjuvant therapy post HSCT. This approach is currently limited to the 20% of patients whose HL is EBV-positive.

Another approach is to enhance the immune function of the patients with biologic response modifiers. High-dose therapy reduces the tumor burden, which renders this strategy more effective. In children with neuroblastoma, the administration of *cis*-retinoic acid improved the outcome after ASCT.²² IFN- α has been used alone or in combination with other biologic agents after HSCT. Klingemann *et al.*²³ first reported the use of IFN- α post HSCT in adults with hematologic malignancies. In this dose escalation study, 14 adult patients (11 were allogeneic transplant recipients) at high risk for relapse received daily treatment for a median of 60 days. The starting dose was 0.5×10^6 U/m². Doses above 1.0×10^6 U/m²/dose were associated with excessive myelosuppression and constitutional symptoms. In another series of lymphoma patients, IFN-2b was started at a dose of 1×10^6 U/m² s.c. three times a week, escalating monthly to 3×10^6 U/m²/dose. Treatment was planned for a total of 6 months.²⁴ Interferon was well tolerated and hematologic toxicity was transient. The mean maximal dose of IFN was 2×10^6 IU/m², similar to that achieved in our patients. Improvement in OS was seen in non-Hodgkin's lymphoma (NHL) patients. Only three of 11 HL were treated and details of response were not described.

The use of IFN- α as salvage therapy after ASCT has also been reported. Deschler *et al.*²⁵ reported a complete remission in an NHL patient, who failed two prior stem

cell transplants and abdominal irradiation. Maloisel *et al.*¹⁴ used IFN- α in seven patients with refractory HL, including those who had relapsed after ASCT, and observed a response in three of them.

In our group of patients, IFN- α was well tolerated, even though it was started soon after ASCT. We began at a dose lower than that reported by others, but were able to escalate treatment intensity within 2–3 months. The median duration of 12 months is longer than that in other series. In animal models, low-dose prolonged interferon exposure was critical in antiangiogenesis and tumor control, whereas high-dose, intermittent therapy was not as effective.²⁶ Even though most of our patients had multiple adverse factors, compatible with the intermediate and worst prognostic risk groups defined by the German–Austrian trial,²⁷ their outcome reported here compares favorably with other pediatric series of autologous ASCT.²⁻⁶ It is possible that giving low-dose IFN- α for an extended period of time post ASCT contribute to better disease control. Recently, novel agents such as gemcitabine, vinorelbine and rituximab were shown to be effective in retrieval therapy of HL.²⁸ Three of our patients received some of these agents, which might have consolidated their remission before ASCT. In addition, two patients received other therapy post-ASCT (local irradiation and cytotoxic T-cell infusion) that may be confounding the interpretation of our result.

Survival data in a one-arm, single institution study should always be interpreted with caution. Although selection bias is unlikely as all consecutive patients undergoing ASCT are reported, the study is retrospective in nature and includes a relatively small number of patients. The dose and duration of IFN- α treatment were not entirely uniform. In addition, our patients are still at some risk of relapse, although most are past the period of greatest risk of disease recurrence. In the two largest series of HSCT in pediatric HL, the median times to relapse were 6 and 23.6 months, respectively.^{3,4} The median observation time of our patients is over 5 years, and all survivors have been followed for at least 2 years.

In summary, we found that IFN- α can be safely administered to pediatric HL patients after ASCT. Gradual dose escalation is possible in the majority of the patients. The optimal dose, duration of therapy and the long-term benefit of this treatment approach require further evaluation. It is of note that the Children Oncology Group in the US is conducting a randomized study to evaluate the immunotherapy (using interferon- γ , interleukin-2 and cyclosporin) following ASCT. Furthermore, given the relatively small number of pediatric patients with relapsed or refractory HL, it will be useful to develop surrogate measures of efficacy (e.g., changes in metabolic activity or gene expression profiles of lymphoma cells) as alternate end points to evaluate post-transplant treatment strategies.

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