

High-dose chemotherapy

A dose escalation study for salvage chemotherapy in patients with refractory lymphoma prior to high-dose myeloablative therapy with stem cell transplantation

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Summary:

Chemosensitive response prior to transplantation has been shown to be most significant for survival post transplant. To estimate toxicity of a dose-intensive regimen that was to improve chemosensitive response rate, 15 patients with primary refractory lymphoma were enrolled in dose escalation of pre-transplant salvage chemotherapy. The first cycle had a fixed dose of ifosfamide 6 g/m² and mitoxantrone 12 mg/m², with arabinosyl cytosine (Ara-C) 2 g/m², and methylprednisolone 2.0 g. Each cycle of the second and third had cisplatin 90 mg/m², Ara-C 6 g/m², methylprednisolone 2.0 g, and escalated doses of ifosfamide from 7.5 g/m² to 15 g/m² and mitoxantrone from 16 to 28 mg/m². Blood stem cells were collected before the second cycle and $\geq 3 \times 10^6$ CD34 cells/kg were infused 2 days after the second and third cycles, respectively. The maximum tolerated doses of ifosfamide and mitoxantrone were 11.25 g/m² and 16 mg/m², respectively. Acute renal failure and bacterial infection occurred as non-hematologic dose limiting toxicities. Eleven patients completed therapy. Five patients achieved complete remission and five had partial remission. Nine patients received autologous and four received allogeneic transplants. Currently, six are alive without evidence of disease, with a 3-year survival of 40%. Although preliminary, the regimen suggests acceptable toxicity and significant activity that warrants further study.

Bone Marrow Transplantation (2002) 29, 647–652. DOI: 10.1038/sj/bmt/1703533

Keywords: primary refractory lymphoma; dose intensive therapy

Survival of patients with lymphoma treated with autologous stem cell transplantation (ASCT) is influenced by response to pre-transplant salvage therapy. For patients with aggressive non-Hodgkin's lymphoma (NHL) at relapse, sensitivity to standard-dose salvage chemotherapy has been shown to be the most important variable for survival post transplant.^{1–2} Pre-transplant disease status of patients with Hodgkin's disease (HD) at first relapse, reflecting sensitivity to chemotherapy, has been shown to be an important prognostic factor for survival after ASCT.^{3–5} Likewise, primary refractory patients with aggressive non-Hodgkin's lymphoma unresponsive to secondary therapy had a poor outcome with a median duration of survival of 6 months and no measurable long-term event-free survival.^{6,7}

In the current study of dose escalation in patients with primary refractory lymphoma, a maximum tolerated dose of both ifosfamide and mitoxantrone was sought, before testing the hypothesis that dose-intensive salvage chemotherapy increases remission rates prior to transplantation. After the intensive salvage treatment, patients went on to receive ablative therapy with transplantation. Dose escalation of ifosfamide and mitoxantrone was based on the linear dose–response curve in the therapeutic range and non-overlapping toxicity.^{8,9} Peripheral blood stem cells (PBSC) harvested immediately before the second cycle were used to support two subsequent cycles of treatment to reduce the extent of hematologic toxicity, thereby allowing timely administration of therapy without delay, and later for transplantation.^{10–12} In the present report, we describe toxicities and preliminary response data of the 15 patients.

Patients and methods

Patients

The study was conducted between June 1997 and June 2000, and the patients were followed to December 2000. Patients with either NHL or HD were eligible if they failed to achieve complete remission on induction therapy. The institutional review board of the College of Medicine, the University of Iowa, approved the study and all patients

Table 1 Regimen

Day	1	2	3	4	6
<i>First cycle</i>					
Ifosfamide 2 g/m ² /day with mesna	X	X	X		
Mitoxantrone 12 mg/m ²	X				
Ara-C 2 g/m ²				X	
Methylprednisolone 500 mg/day	X	X	X	X	
<i>Second and third cycles (each cycle)</i>					
Ifosfamide ^a with mesna	X	X	X		
Mitoxantrone ^a	X				
Cisplatin 30 mg/m ² /day	X	X	X		
Ara-C 3 g/m ² every 12 h				XX	
Methylprednisolone 500 mg/day	X	X	X	X	
Infusion of blood stem cells					X

See text for the details of chemotherapy.

^aSee Table 2 for dose escalation.

gave written informed consent at the time of study entry. Eligibility included age between 17 and 60 years old; performance score $\geq 50\%$; diffusion capacity $>60\%$, FEV₁ >1.5 l, or PaO₂ >60 mmHg; left ventricular ejection fraction $>55\%$; serum creatinine <1.5 times normal; bilirubin or transaminases <3 times normal not related to tumor; cumulative dose of doxorubicin <300 mg/m²; no prior therapy with ifosfamide or mitoxantrone containing regimen(s); no evidence of disease in marrow or blood; no active infection.

Treatment regimen (Tables 1 and 2)

Three cycles of therapy were planned at 4-week intervals or sooner if platelets increased to $\geq 75 \times 10^9/l$. Treatment was delayed until the absolute neutrophil count (ANC) recovered to $\geq 2 \times 10^9/l$ and the platelet count to $\geq 75 \times 10^9/l$. (1) First cycle: ifosfamide 2 g/m²/day i.v. over 4 h on days 1–3, with mesna 1.5 g/m² i.v. and a second dose of mesna 500 mg/m² i.v. 4 h after the dose; mitoxantrone 12 mg/m² bolus i.v. immediately after ifosfamide on day 1; arabinosyl cytosine (Ara-C) 2 g/m² i.v. over 3 h on day 4, 24 h after the last ifosfamide; methylprednisolone 500 mg/day i.v. over 30 min on days 1–4. (2) The second and third cycles had a dose escalation of ifosfamide and mitoxantrone: ifosfamide i.v. over 4 h on days 1–3, with mesna; mitoxantrone i.v. immediately after ifosfamide on day 1; cisplatin 30 mg/m² i.v. over 4 h on days 1–3, starting 2 h after ifosfamide, along with 0.9% NaCl i.v. at 250 cc/h for

Table 2 Dose escalation table

Dose level	Ifosfamide (g/m ²) $\times 3$ days	Mitoxantrone (mg/m ²)
1	2.5 (total dose 7.5)	16
2	3.75 (11.25)	16
3	5 (15)	16
4	5 (15)	20
5	5 (15)	24
6	5 (15)	28

the 3 days; 2 doses of Ara-C 3 g/m² i.v. over 3 h every 12 h on day 4, 24 h after the last ifosfamide; methylprednisolone 500 mg i.v. on days 1–4.

The dose of ifosfamide was increased as 7.5 g/m², 11.25 g/m² and 15 g/m². The dose of mitoxantrone was to be increased by 4 mg/m², from 16 mg/m² to 28 mg/m². Patients received three courses of therapy at the same dose level for each course. Toxicities were graded using the National Cancer Institute common toxicity criteria. Dose limiting toxicity (DLT) was defined if grade 4 non-hematologic toxicity occurred, the platelet count $<75 \times 10^9/l$ or ANC $<2 \times 10^9/l$ in 4 weeks after each cycle. Dose escalation and patient accrual followed a standard phase I study design. Cohorts of three patients were enrolled at each dose level. If no patients in a cohort experienced DLT during a 4-week observation period, the dose was escalated and the next cohort was accrued. If one of three patients experienced DLT, a second cohort of three was added at the same dose level. If two patients experienced a DLT at the same dose level, no further patients were treated at the dose level and an additional cohort of three patients was entered at the previous dose level. Once the maximum tolerated dose (MTD) was established, additional patients could be entered to define toxicity further at this dose level. If a patient who experienced DLT recovered fully from the toxicity, the patient could resume therapy at the previous level. Patients who did not recover fully from DLT in 4 weeks were taken off study.

Peripheral blood stem cells and supportive care

PBSC were mobilized when patients were recovering from the first cycle, with a daily granulocyte colony-stimulating factor (G-CSF) at 10 μ g/kg. PBSC of 9×10^6 CD34⁺ cells/kg of patient's ideal body weight were collected. Apheresed products were cryopreserved as three separate aliquots, with $>3 \times 10^6$ CD34⁺ cells/kg per each. PBSC were infused on day 6 of both the second and third cycles. The remaining aliquot was used for autologous transplantation.

Prophylactic ofloxacin 400 mg/day was used during neutropenia. Sulfamethoxazole 800 mg–trimethoprim 160 mg twice a day and itraconazole 200 mg twice a day were also given for 10 days of each cycle. G-CSF was started day 10 of each cycle until the ANC $>2 \times 10^9/l$. Both hemoglobin and platelets were maintained at ≥ 10 g/dl and $\geq 10 \times 10^9/l$, respectively. All blood products were filtered and irradiated to 3000 cGy.

Stem cell transplantation

Transplantation was done within 4 weeks after the last cycle of therapy. The BVAC regimen for ASCT was administered as previously described:¹³ carmustine (BCNU) 600 mg/m² i.v. day –8; etoposide 400 mg/m²/day i.v. days –7 to –4; Ara-C 3 g/m² i.v. every 12 h $\times 8$ doses, starting day –7; cyclophosphamide 3.6 g/m² i.v. day –2. For allogeneic bone marrow transplantation, the TBI-BVAC regimen was administered as previously described:¹⁴ total body irradiation of 1200 cGy in six fractions with lung shielding to a total dose of 800 cGy days –8, –7, –6; BCNU 300 mg/m² i.v. day –5; etoposide

600 mg/m²/day i.v. days -3, -2; Ara-C 2 g/m² i.v. every 12 h × 4 doses starting day -4; cyclophosphamide 3.6 g/m² i.v. day -2.

Response evaluation and survival

Response was evaluated by the methods of Miller *et al*¹⁵ and Cheson *et al*.¹⁶ Since all events led to death, resulting in almost identical overall survival and event-free survival, only the event-free survival was presented, calculated by the product limit estimate of the Kaplan–Meier method. Events were defined as death from any cause, or relapse in patients who survived the first 28 days after the transplant.

Results

Patients and dose escalation

Patient characteristics are shown in Table 3. The median age was 37 years (range, 20 to 56 years) and the median Karnofsky performance score at study entry was 70% (range, 50% to 80%). All patients received the first two cycles of therapy. Four patients did not receive the third cycle: two because of progressive disease (one diffuse large B cell lymphoma (DLCL), one HD); one because of acute renal failure at dose level 3; one because of depression. Three patients completed dose level 1. At dose level 2, six patients were initially accrued because of one episode of grade 3 central nervous system toxicity. At dose level 3,

one episode of acute renal failure and a fatal bacterial sepsis occurred. Following these two episodes, three more patients were treated at dose level 2, resulting in no further DLT. Therefore, dose level 2 was established as MTD (11.25 g/m² for ifosfamide and 16 mg/m² for mitoxantrone).

Non-hematologic toxicities

One patient developed oliguric acute renal failure at dose level 3, after ifosfamide 15 g/m² was concurrently given with vancomycin and gentamicin for a wound infection. His initial renal function was normal with a serum creatinine of 0.8 mg%. No patients at dose level 2 experienced >grade 2 genitourinary toxicities except for three cases of a mild increase in creatinine and three cases of brief microscopic hematuria. Nine patients (60%) suffered from grades ≤3 mucositis. The median duration of mucositis was 5 days (range, 2 to 13 days). No patients experienced hepatobiliary toxicity. One patient (7%) developed grade 3 toxicity of the nervous system with ataxia and disorientation at dose level 2. Two patients (13%) experienced mild to moderate parasthesia and mild hearing loss. There were no cases of cardiopulmonary toxicity prior to transplantation.

Hematologic toxicity and infection

The median duration of ANC <0.5 × 10⁹/l at dose level 1 was 4 days (range, 4–6 days) after the first cycle; 7 days after both second and third cycles (range, 6–12 days; 6–7

Table 3 Patient characteristics

UPN	Sex	Age	Diagnosis	Stage	Initial therapy	Response -I	Dose	Response -S	Transplant	Response -T	Status	Cause of death
1	F	20	DLCL	III-B (bulky)	CHOP × 8, DHAP × 2, IF XRT 2100 cGy	PR	1	CR	AU	CR	Alive	
2	M	54	MCL	II-A (bulky)	CHOP × 4	R	1	PR	AU	CR	Alive	
3	M	28	HD, NS	III-B	MOPP-ABV × 8, mediastinal XRT 2000cGy	R	1	P	AL	NA	Dead	IPS
4	M	32	HD, s-NS	IV-A, (bulky-mediastinal)	ABVD × 6	R	2	PR	AU	PR	Dead	IPS
5	M	21	HD, s-NS	II-B, (bulky-mediastinal)	ABVD × 5	R	2	PR	AL	CR	Alive	
6	M	53	DLCL	IV-B, (bulky-abdominal)	CHOP × 6, DHAP × 2,	R	2	P	AU	PR	Dead	Multi-organ failure
7	F	55	DLCL	III-B	CHOP × 7	R	2	PR	AL	R	Dead	P
8	M	27	HD, NS	II-E	ABVD × 6, mantle XRT3500 cGy	PR	2	P	AU	R	Dead	P
9	M	38	HD, NS	III-A, (bulky)	MOPP-ABV × 5	PR	2	CR	AU	CR	Alive	
10	M	47	HD, s-NS	II-B	ABVD × 6, IF XRT 3600cGy	R	3	CR	AU	CR	Alive	
11	M	24	DLCL	II-A, (bulky-mediastinal)	CHOP × 4, mediastinal XRT 4500 cGy,	PR	3	NA	NA	NA	Dead	Sepsis
12	M	43	HD, NS	IV-B	ABVD × 5, mantle XRT 3500cGy	R	3	NA	NA	NA	Dead	Renal failure
13	F	52	DLCL	IV-B	CHOP × 6, mediastinal XRT 4100 cGY	PR	2	CR	AU	CR	Dead	IPS
14	M	56	DLCL	IV-B, (bulky-mediastinal)	CNOP × 5, IF XRT 3500 cGy	PR	2	CR	AU	NA	Dead	Multi-organ failure
15	M	37	DLCL	IV-B	CHOP × 3	R	2	PR	AL	CR	Alive	

F = female; M = male; MCL = mantle cell lymphoma; NS = nodular sclerosing type; s-NS = syncytial variant nodular sclerosing type; IF = involved field; Response-I = initial response; Dose = dose level; Response-S: response to the study regimen; Response-T = response to transplantation; R = refractory; P = progressive; NA = not available; AU = autologous; AL = allogeneic.

days, respectively). The median duration of platelet counts $<20 \times 10^9/l$ was 8 days (range, 3–15 days) after the second and third cycles. The median time to an ANC $>2 \times 10^9/l$ after infusion of blood stem cells was 13 days (range, 8–21 days); the median time for a platelet to increase to $>75 \times 10^9/l$ was 22 days (range, 18–26 days). Eight of 41 cycles of therapy (20%) were complicated by infectious episodes. One patient developed a fatal bilateral pneumonia with *Staphylococcus aureus* during neutropenia after the third cycle at dose level 3. There were no cases of invasive fungal infection.

Response

Eleven patients (73%) completed three cycles of therapy. Five patients (33%) achieved complete remission (CR) and five (33%) had partial remission (PR), with an overall response rate of 66% by the intent-to-treat principle. Three patients with DLCL, and two with HD had a CR. Two with HD, one with mantle cell lymphoma and two with DLCL had a PR. At dose level 1, there was one CR, one PR and one progressive disease; at level 2, three CR, four PR, two progressive disease; at level 3, one CR and two not evaluated for response because of episodes of DLT.

Transplant therapy

Thirteen patients underwent transplantation. Nine patients underwent ablative therapy with the BVAC regimen and ASCT. Two patients died of multi-organ failure on day 13 and 38 of the transplant, respectively. Two patients died of idiopathic pneumonia syndrome (IPS), 60 and 78 days after transplantation, respectively. One patient with DLCL had a relapse on day 72 post transplant. Four patients received allogeneic stem cell transplantation, using unrelated donors ($n = 3$) and a matched sibling ($n = 1$). One unrelated recipient died of IPS on day 8 of the transplant. The second unrelated recipient with DLCL died of progressive disease on day 27. The three patients with IPS had received prior mediastinal irradiation before the current therapy. Currently, six patients are alive without evidence of disease, with a 3-year event-free survival rate of 40% (Figure 1a). The 3-year event-free survival for the patients who underwent transplantation was 51% (Figure 1b).

Discussion

As proof of principle, the present study shows that active chemotherapeutic agents can be dose-intensified and combined for salvage chemotherapy for patients with refractory lymphoma. The MTD of both ifosfamide and mitoxantrone was identified in the current regimen that made use of blood stem cells to reduce dose-limiting pancytopenia. Ifosfamide at 11.25 g/m^2 ($3.75 \text{ g/m}^2 \times 3$ days) and mitoxantrone at 16 mg/m^2 in combination with other agents were tolerated well, albeit a further increase in ifosfamide to 15 g/m^2 ($5 \text{ g/m}^2/\text{day} \times 3$ days) resulted in two episodes of dose limiting toxicity. The dose of mitoxantrone was not escalated further from the baseline dose of 16 mg/m^2 due to the study scheme. Although renal failure may have been triggered or

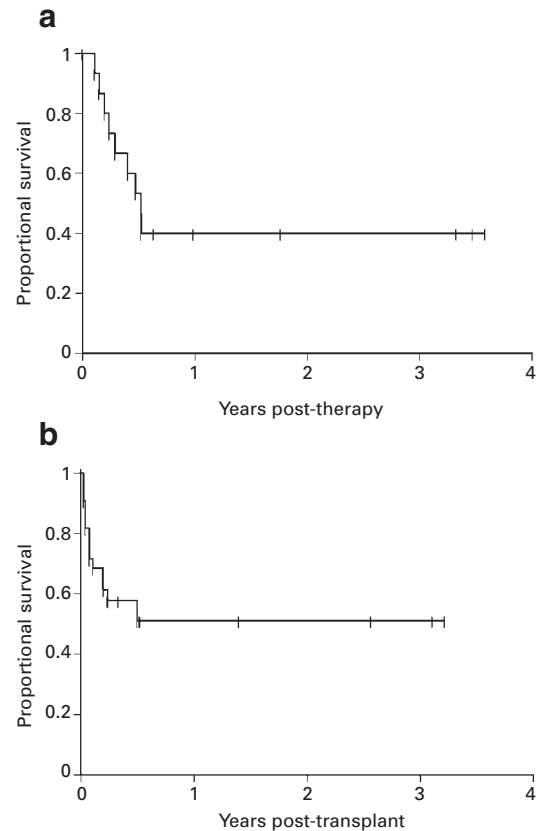


Figure 1 Kaplan-Meier 3-year event-free survival rate. (a) All patients; (b) transplanted patients.

exacerbated by the combination with cisplatin and concurrent use of an aminoglycoside antibiotic, it appears to be similar to reported episodes of acute renal failure at doses ranging from 12 g/m^2 to 16 g/m^2 .^{17–19} One other episode of DLT occurred as fatal septic pneumonia with *Staphylococcus aureus* during neutropenia despite the use of growth factor-primed stem cells. It remains to be seen whether the regimen increases the likelihood of infection during neutropenia because of the combination of high-dose methylprednisolone with mucolytic agents, ie Ara-C and mitoxantrone.

The three fatal cases of IPS post transplant may have been related to prior chest/mediastinal irradiation,²⁰ the current study regimen, transplant regimens or a combination of these treatments. Although the high dose of BCNU (600 mg/m^2) in the BVAC regimen and TBI of 1200 cGy and BCNU of 300 mg/m^2 of the TBI-BVAC regimen must have contributed to the lung injury,^{21,22} a careful prospective phase II study is necessary to elucidate the extent of pulmonary toxicity of the present study.

The response rate of 66% of the present study is encouraging, comparing favorably with published phase II studies, although it requires further study since it was a phase I investigation and there was a potential selection bias such as exclusion of patients who had evidence of disease in marrow or blood.^{7,22–25} Although a number of phase II studies have shown that high-dose ablative therapy with stem cell transplantation was effective in patients with disease sensitive to pre-transplant salvage therapy,^{1–7,26} patients

with resistant lymphoma, particularly those with primary refractory disease, have poor survival rates.^{6,7,27,28} In these patients, sensitivity of the tumor may have been reduced to below the 4-log kill with standard dose, which may not allow cure by a three- to five-fold increase in dose in the majority of patients, typically used in stem cell transplantation.²⁹ Similar to previous reports, the current study suggests that patients with refractory disease that is partially sensitive, could respond better to therapy with higher dose intensity than that used in the conventional salvage treatment, probably by achieving a higher log kill than standard salvage therapy.^{30,31} Responding patients would then be able to undergo stem cell transplantation with intent for cure by reducing tumor cells further to more than a 4-log overall tumor kill.

Our preliminary study lends support for further investigation of a dose-intensive approach for patients with primary refractory lymphoma. Questions that need to be answered are what chemotherapeutic agents and what combinations are best suited to this approach, how toxicity could be reduced and what sequence of therapy would be most appropriate. Since there may not be a further survival benefit from high dose of BCNU at 600 mg/m² or by TBI containing regimen, as suggested by previous transplant studies, patients who have received a significant amount of chest or mediastinal radiation may require an ablative regimen with a reduced dose of BCNU or non-TBI-based regimens for transplantation, to prevent IPS post-transplant. A phase II study of the present regimen is currently underway, which will provide an answer concerning its contribution to an overall survival benefit in patients with refractory lymphoma.

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