Tandem high-dose therapy followed by autologous stem-cell transplantation for refractory or relapsed high grade non-Hodgkin's lymphoma with poor prognosis factors: a prospective pilot study

We conducted a tandem autologous stem cell transplantation procedure for patients with relapsed or refractory high-grade non-Hodgkin's lymphoma (HGNHL) or with transformation of indolent lymphoma (n=15). These patients had poor prognosis factors. The procedure was well tolerated, ten patients were in complete remission. Overall survival rate is 67%.

Many salvage chemotherapy regimens have been proposed for patients with high-grade non-Hodgkin's lymphoma (HGNHL) with refractory or early relapsing disease.

Because one line of high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is not sufficient to cure a majority of those patients,[1] we have performed a pilot study including a tandem HDT followed by ASCT. Patients with aggressive transformation of indolent lymphoma and poor prognosis factor were also included.

Patients with refractory or with early relapse HGNHL (time from diagnosis to relapse less than 1 year) started the procedure with a salvage second line chemotherapy: DHAP,[2] ESHAP[3] or HD-Ara-C and idarubicin.[4] Patients with aggressive transformation of indolent lymphoma were treated with HD-CHOP chemotherapy. Peripheral blood stem-cells were collected under granulocyte colony-stimulating factor (G-CSF) stimulation after salvage chemotherapy.

The first HDT was performed in a standard single hospital room with isolation procedures, 30-60 days after the last course of salvage chemotherapy. The second HDT was scheduled 30-60 days after the first one. Patients were housed in a sterile unit.

The conditioning regimens for the first HDT was: mitoxantrone 45 mg/m^2 IV d1 and Ara-C 1 g/m^2/12h IV d1-d4. Total body irradiation (TBI) (12 Gy: 2Gy × 2d for 3 days) and cyclophosphamide (60 mg/kg × 2d. IV d1-d4) was used for the second.[5] Response assessment was evaluated after salvage chemotherapy and after the second HDT.[6] No evaluation of the response was sheduled after the first HDT. The final evaluation was performed 2 months after the second HDT. The aim of the study was to evaluate the feasibility and the toxicity of the program and, secondarily, the overall survival (OS) (from the date of beginning salvage chemotherapy).

Fifteen patients were included in the procedure (Table 1). Their median age was 46 years (range 30-58). The patients with HGNHL were all initially treated at diagnosis with standard CHOP or HD-CHOP chemotherapy. All but 2 patients received DHAP, ESHAP or HD-Ara-C and idarubicin as salvage chemotherapy. Patient #6 was treated with HD-CHOP because of renal insufficiency.

Patient #7 with an initial Burkitt-like lymphoma diagnosis was treated with 2×COPADM and 2×CYVE chemotherapy.[7] Two courses of MIME chemotherapy[8] were administered to patient #10 because of refractory disease after salvage chemotherapy.

For the second HDT, patient #9 was treated with BEAM[9] because previous irradiation precluded TBI.

For twelve patients, a single peripheral blood stem cell collection was sufficient to perform two ASCT. For the three others, a second mobilization procedure were performed after the first ASCT upon G-CSF stimulation.

The duration of hospitalization was similar for the first and the second ASCT (20 vs. 18.4 days). No major toxic effect was reported during the whole procedure. After salvage chemotherapy, four patients achieved a complete response (CR), six a complete response/unconfirmed (Cru) and four a partial response (PR). Only

Table 1. Characteristics of patients.

Patients	*Age/sex*	*Initial diagnosis*	*Prior therapy*	*R 1*	*Extra-nodal*	*IPI*	*Stage*	*Salv. chemoth.*	*R 2*	*Cond. Reg.1*	*Cond. Reg.2*	*R 3*	*Status (months)*
1	49/f	HGNHL	8×CHOP	CR	BM	Inter High	IV	3×Ida- Cytarabine	PR	Nov-Ara-C	TBI-Cy	CR	Dead (14)
2	53/m	HGNHL-T	4×CHOP	Pr	–	Inter High	III	3×Ida- Cytarabine	Ref	Nov-Ara-C	TBI-Cy	CR	Dead (13)
3	53/m	HGNHL	3×HD-CHOP	CR	–	Inter High	III	2×ESHAP	CR	Nov-Ara-C	TBI-Cy	CR	Dead (13.5)
4	41/m	HGNHL-T	8×CHOP	CR	BM	High	IV	3×ESHAP	PR	Nov-Ara-C	TBI-Cy	Ref	Dead (9)
5	39/f	HGNHL	3×HD-CHOP	Ref	Ureter, vagina	Inter low	IV	3×ESHAP	Cru	Nov-Ara-C	TBI-Cy	CR	CR (36.5)
6	30/m	HGNHL	1×CHOP	Pr	Liver	High	IV	2×HD CHOP	Cru	Nov-Ara-C	TBI-Cy	CR	CR (20)
7	58/m	HGNHL Burkitt-like	7×CHOP	Pr	CNS, BM	High	IV	2×COPADM-CYVE	CR	Nov-Ara-C	TBI-Cy	CR	CR (31.5)
8	46/f	HGNHL	8×CHOP	CR	–	Low	II	2×DHAP	CR	Nov-Ara-C	TBI-Cy	CR	CR(22)
9	49/m	HGNHL	2×CHOP	Ref	Bone	Inter High	IV	1×DHAP	Cru	Nov-Ara-C	BEAM	CR	CR (20)
10	46/m	HGNHL	8×CHOP	CR	–	Inter High	III	2×DHAP; 2×MIME	Cru	Nov-Ara-C	TBI-Cy	CR	CR (19)
11	51/m	WALD. transf.	None	–	BM	Inter High	IV	2×HD CHOP	CR	Nov-Ara-C	TBI-Cy	CR	CR (14)
12	49/m	Foll. transf.	None	–	Liver	Inter low	IV	2×HD CHOP	Cru	Nov-Ara-C	TBI-Cy	CR	CR (44.5)
13	37/m	Foll. transf.	None	–	BM	Inter High	IV	4×HD CHOP	CRu	Nov-Ara-C	TBI-Cy	CR	CR(54.7)
14	41/m	WALD. transf.	None	–	Bone	Inter High	IV	2×HD CHOP	PR	Nov-Ara-C	Dead	Dead	Dead
15	38/m	Foll. transf.	2×CHOP	Pr	–	Inter low	III	2×ESHAP	PR	Nov-Ara-C	TBI-Cy	CR	CR (32.5)

Abbreviations: HGNHL: high-grade non-Hodgkin's lymphoma; HGNHL-T: high-grade Non-Hodgkin's lymphoma T phenotype; Wald. Transf.: histologic aggressive transformation of Waldenström's disease; Foll transf.: histological aggressive transformation of indolent follicular lymphoma; CR: complete remission; Prog: progressive disease; Ref: refractory disease; BM: bone marrow; CNS: central nervous system; PR: partial response; CRu: complete response/unconfirmed; FU: follow-up; R1: response after prior chemotherapy; R2: response after salvage chemotherapy; R3: response at the final evaluation.

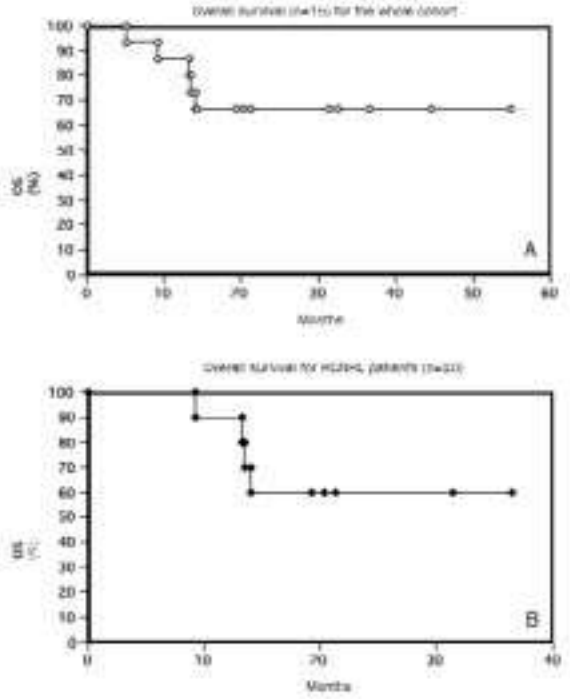

Figure 1. Survival curves were computed according to the method of Kaplan-Meier. 1a: Survival from the beginning of the procedure for the whole cohort (n = 15). 1b: Survival from the beginning of the procedure for the initial HGNHL group (n = 10).

one patient had refractory disease (patient #2). Fourteen patients have undergone the whole procedure; only patient #14 died because of disease progression before the second ASCT. Thirteen patients were in CR (87%) after the second ASCT. Only one patient had refractory disease. All patients in CRu after salvage chemotherapy and two of the four patients in PR achieved a CR. Patient #2 with refractory disease achieved a CR.

The median follow-up duration is 20 months (range 5-55) and the 4 year (OS rate is 67%). For the limited cohort of HGNHL patients (n=10), the median follow-up is 19 months (range 9-36.5) and OS is 60%. Three patients in CR at the date of final evaluation (patients #1, 2, and 3) ultimately relapsed and died.

In this study, we chose to perform a myeloablative conditioning regimen only for the second HDT in order to reduce drug toxicity. The aim of the first HDT was to provide additional tumor reduction before the first myeloablative regimen. The regimen used for this purpose was chosen because of its low toxicity rate and because 45 mg/m^2 of mitoxantrone appears to be an interesting compromise between toxicity and efficacy.[10]

This pilot study, although on a small number of patients but with a poor prognosis, shows the feasibility (fourteen patients have undergone the whole procedure) and the low toxicity rate of the procedure. A CR was achieved in thirteen patients but four relapsed within 9 months after the second transplant. No relapse or death has been documented after this 9-month period. OS curves confirm these results with a plateau occurring at 9 months. The OS rates (67% for the whole cohort and 60% for patients with initial HGNHL) are encouraging. These results suggest that tandem HDT with autologous support including a second myeloablative regimen may be an attractive alternative therapeutic option for chemotherapy-sensitive HGNHL in early relapse after conventional treatment as well as for transformed low-grade NHL. A randomized trial versus simple HDT with ASCT should be performed to demonstrate the superiority of this tandem HDT.

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