Treatment of High-Risk T-NHL with Stem Cell Transplantation: A Single Center Experience

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Abstract Prognosis of peripheral and other advanced T cell lymphomas is poor. 20 patients with a median age of 46.4 (range 20.5–64.1) years were treated with autoSCT ($n = 6$) or alloSCT ($n = 14$) from 1996 to 2013. All patients were at high risk either due to the IPI-score or to the fact that SCT was part of a salvage therapy. Conditioning prior to alloSCT was myeloablative in seven cases (50 %). The patients were pretreated with 8.5 (median, range 2–38) cycles of chemotherapy. Ten patients are alive in CR after a median follow-up of 1.3 years (range 0.1–13.3). OS was 53 % after one and 40 % after 10 years. Best survival was reached after related alloSCT (80 % at 10 years) compared to other modalities. GvHD did not influence survival. AlloSCT from related donors can cure patients from T-cell lymphomas. Unrelated alloSCT or high-dose therapy and autoSCT are an option for patients without a familiar donor.

Keywords T-cell derived non-Hodgkin's lymphoma · Autologous stem cell transplantation · Allogeneic stem cell transplantation · Graft versus lymphoma effects

Introduction

T-cell derived non-Hodgkin's lymphomas are a rare and heterogeneous group of diseases [1]. Peripheral T-cell lymphomas (PTCLs) are mostly associated with a poor prognosis. The standard treatment protocol for B-cell lymphomas (CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone) shows inferior results in PTCLs compared to results in analog B-cell lymphomas [2]. The 5-year survival rates range between 30 and 40 % in most trials including the most common entities like PTCL, not-otherwise-specified (PTCL-NOS), systemic ALK-negative anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL). Despite a lot of studies evaluating novel therapies convincing alternative treatment schedules are absent [2, 3].

Transplant strategies have been published as a part of the primary treatment and as salvage therapy [4, 5]. The overall survival rates reported after allogeneic transplantation range between 20 and 80 %. There is no clear evidence for superiority of allogeneic (alloSCT) compared to autologous stem cell transplantation (autoSCT) as part of the primary treatment strategy. In general, the outcome following alloSCT seems to be better in nodal vs. extranodal disease, in early vs. advanced disease and in patients with low vs. high international prognostic index (IPI).

Corradini et al. [5] have integrated autoSCT in first line therapy and reported a ten year overall survival (OS) of 55 %. ALK⁺ lymphomas which represented 63 % of the collective achieved better survival results compared to ALK⁻ disease. However, the curves did not show a plateau in both groups. The same group reported a 3-year overall survival of 80 % in younger patients with relapsed PTCL after reduced intensity conditioning (RIC) followed by alloSCT [6]. In a recent update the 12-year overall survival

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dropped to 34 % [7]. However, both investigations included patients with ALK⁺ lymphomas, a disease known for a comparatively good prognosis. Because of the positive data obtained by alloSCT the authors suggested a contribution of graft-versus-lymphoma effects to curing. This hypothesis is supported by the data from Okamura et al. [8] who reported a trend for better survival for patients developing acute GvHD after allo-SCT. The group from Seattle described a 3 year overall survival of 59 % after RIC followed by alloSCT, however, the curve declined to ~30 % after 5 years of follow-up [9].

Schetelig et al. have autografted patients with AITL and reported a 5 years OS of 59 % when autoSCT was performed upfront. There was a trend for an inferior survival after autoSCT as part of a salvage regimen. Overall, there are limited data concerning the significance of transplantation strategies in the treatment of T-cell lymphomas [10].

Patients and Methods

Patients, Diagnoses and Pre-treatment

Eighteen patients with a median age of 46.5 years (range 20.5–64.1) underwent stem cell transplantation for T-cell lymphoma at Greifswald University Hospital between August 1996 and March 2013. Seven patients (35 %) had PTCL, $n = 4$ (20 %) ALCL, $n = 3$ (15 %) AITL, and $n = 1$ (5 %) each advanced Sézary-syndrome, primary cutaneous aggressive epidermotropic T-cell lymphoma, TLBL, extranodal NK/T-cell lymphoma and T-PLL as the underlying diagnosis. The median Ann Arbor stage at diagnosis was 4 (range 1–4) and 45 % ($n = 9$) had B-symptoms. The median IPI was 2 (range 0–3) and $n = 14$ patients (70 %) suffered from extranodal lymphoma. Fourteen patients (70 %) had an IPI of ≥ 2 indicating a disease with increased risk (Table 2). Only 1/20 patient (5 %, patient #10, Table 1) scored positive for the expression of the anaplastic lymphoma kinase protein (ALK⁺). The transplant was performed as a part of the

salvage strategy. Median pre-treatment prior to conditioning and SCT was 8.5 (median, range 2–38) cycles of chemotherapy within 2 (median, range 1–4) different regimens. According to the pre-treatment the transplantation had to be considered as a salvage strategy in 17 cases (85 %). According to the IPI and pre-treatment all patients had to be considered as high risk (Tables 1, 2).

At the time of stem cell transplantation, the disease status was a complete remission in $n = 10$ patients (50 %) and a partial remission in nine patients (45 %). One patient (5 %) proceeded with progressive lymphoma to transplantation (Table 2).

Conditioning and Stem Cell Transplantation

Generally, allogeneic stem cell transplantation was the preferred concept, however, six (30 %) patients were treated with high-dose therapy followed by autologous stem cell reinfusion. Two of these patients were autografted before the allogeneic transplantation was established at our institution. Three patients were ineligible for an allograft and one patient was treated according the SMILE-protocol [11].

On average, the patients underwent stem cell transplantation 7.9 months (median, range 2.6–85.1) after primary diagnosis of lymphoma. Fourteen patients were allografted from HLA-identical siblings ($n = 5.20$ %) or matched unrelated donors ($n = 9.45$ %). Risk factors were an HLA-A and HLA-B mismatch and a CMV[−] donor/CMV⁺ recipient constellation in one case each and a female donor/male recipient constellation in two cases. Six patients (30 %) were autografted. All patients received G-CSF mobilised peripheral stem cells. The median dose was $5.9 \cdot 10^6$ CD34⁺-cells/KG bodyweight (range 2.6–10.2) for alloSCT and $3.7 \cdot 10^6$ CD34⁺-cells/KG bodyweight (range 2.1–18.4) for autoSCT. High-dose therapy prior to autoSCT was Busulfan/Cyclophosphamide in three cases and BEAM, VIC and Busulfan/Thiotepa in one case each [12]. Conditioning prior to alloSCT was Busulfan/VP-16/Cyclophosphamide in five cases, Treosulfan/Fludarabine in three cases, and TBI/Fludarabine in two cases [13, 14, 15]. Busulfan/Fludarabine, Busulfan/Cyclophosphamide, Melphalan/Fludarabine and Busulfan/Melphalan/Fludarabine were given in one case each [16]. Conditioning was myeloablative in seven cases (50 %) of fourteen allografts. Toxicity-reduced conditioning protocols were chosen according to the medical pre-conditions of the patient. In eleven patients an antibody (alemtuzumab: $n = 10$, anti-thymocyte globulin: $n = 1$) was added. Further GvHD-prophylaxis consisted of cyclosporine-A, either in conjunction with short course methotrexate ($n = 12$) or with mycophenolate mofetil ($n = 2$), depending on the conditioning protocol. In general, it was scheduled to discontinue GvHD prophylaxis between day +100 and +120.

Table 1 Regimen-related toxicity according the Bearman-criteria

Toxicity/degree	0	I°	II°	III°	IV°
Cardiac	20	0	0	0	0
Bladder	19	0	1	0	0
Renal	12	7	1	0	0
Pulmonary	20	0	0	0	0
Hepatic	12	8	0	0	0
CNS	19	0	1	0	0
Stomatitis	5	3	11	1	0
Gastrointestinal	11	8	1	0	0

Table 2 Patients' characteristics

Patient-#	Age (years)	Gender	Transplant-type/donor	T-NHL (histology)	IPI	CTX-regimen prior to SCT	CTX-regimen prior to SCT	Disease status at SCT	Time DX to SCT (months)
1	46.4	W	Mud	PTCL	3	2	5	CR	19.3
2	45.9	M	Mrd	PTCL	2	3	7	CR	32.4
3	55.8	M	Mrd	AITL	2	2	17	PR	8.5
4	64.1	W	Mud	T-PLL	3	1	38	PR	3.4
5	45.2	M	Mud	Sezary	3	2	22	CR	6.0
6	40.2	M	Mrd	ALCL	1	2	13	PR	60.7
7	59.4	W	Mrd	ALCL	0	2	9	PR	19.1
8	48.7	M	Mud	PTCL	2	4	15	PR	5.7
9	51.7	M	Mud	AITL	3	3	13	CR	14.1
10	42.2	W	Mrd	ALCL	2	2	12	CR	13.4
11	44.6	M	Mud	PTCL	3	2	16	PR	7.2
12	20.5	M	Mud	PTCL	3	3	3	PR	2.6
13	28.5	W	Mud	PTCL	1	8	2	CR	7.4
14	46.4	W	Mud	pceTCL	1	8	2	CR	73.8
15	51.7	M	Autologous	ALCL	0	2	6	CR	85.1
16	44.5	W	Autologous	PTCL	3	2	3	PD	3.2
17	63.6	M	Autologous	PTCL	3	1	2	PR	3.1
18	62.5	M	Autologous	AITL	2	3	3	PR	3.8
19	40.6	M	Autologous	TLBL	2	2	3	CR	4.9
20	50.4	M	Autologous	T/NK-NHL	0	3	9	CR	26.9

Mud matched unrelated donor, *mrd* matched related donor (HLA-identical sibling), *CTX* chemotherapy, *CR* complete remission, *PR* partial remission, *PD* progressive disease, *DX* diagnosis, *pceTCL* primary cutaneous aggressive epidermotropic T-cell lymphoma

Supportive Care, Toxicity and Haematological Recovery

Supportive care and antimicrobial prophylaxis was carried out with quinolones and antimycotics following standard procedures as described [17]. In the case of fever above 38.3 °C broad spectrum antibiotics consisting of ceftazidime or carbapenems in combination with vancomycin, respectively, were initiated after immediate diagnostics following standard procedures. All patients received G-CSF from day +1 after transplantation to stimulate haemopoiesis. Parameters of haematology and clinical chemistry were analysed at least once daily. Erythrocytes were substituted when haemoglobin decreased below 8 mg/dl and platelets were given prophylactically in case of counts below than 10/nl. The haematological recovery was related to the day of stem cell reinfusion (day 0). Leukocyte engraftment was defined as the first of 3 consecutive days with absolute leukocyte count exceeding 1.0 cells per nl of blood. Steps of platelet count recovery were defined as the first day that the platelet count exceeded 20 and 50 platelets per nl of blood, respectively, independent of platelet transfusions. Acute and chronic GvHD were graded and treated according international standard [18, 19]. Non-haematological toxicity was graded according the

Bearman-criteria and overall and relapse-free survival were calculated using the log-rank test and the Kaplan–Meyer analysis [20].

Statistics

Data were collected using the computer software MS-Office (Microsoft, Munich, Germany) and analysed with GraphPad Prism (GraphPad Software, San Diego, Ca., USA). The statistical tests used were the Mann–Whitney *U*-test and the Kaplan–Meyer survival analysis.

Results

Haematological Parameters

All patients engrafted with 1 leukocyte/nl at day +12.5 (median, range 8–27) after SCT. Median time to 20 platelets/nl independently from transfusions was 12 days (range 7–41). In two cases the platelets did not fall below 20/nl and one patient did not reach platelet engraftment due to complications. Platelet counts above 50/nl occurred at day 15.5 (median, range 8–395) in 18 patients. One patient

died before his platelets reached this step and in one case the data were not available.

Non-haematological Toxicity and GvHD

In general, toxicity was mild to moderate. The leading toxicity was mucositis with a median degree of 2 (range 0–3). Toxicity II° of the bladder, kidney and CNS occurred in one case each. Regimen-related deaths were not seen. Further details are shown in Table 1.

Mild to moderate acute GvHD (grade 1–2) occurred in 4/14 patients (28.6 %) and severe (grade 3) in two patients (14.3 %) after alloSCT. Grade four acute GvHD was not seen. Five patients (35.8 %) developed chronic GvHD, either limited ($n = 3$, 21.4 %) or extensive ($n = 2$, 14.3 %) disease. Neither acute nor chronic GVHD was observed in six patients. No patient died from GvHD.

Relapses, Deaths and Survival

A complete remission after SCT was achieved in 18/20 patients (90.0 %). Two patients (10.0 %) had progressive disease after autoSCT. The median follow-up of all patients was 1.3 years (range 0.1–13.3) after SCT. The overall survival was 53.0 % after 1 year and 40.0 % after 10 years (Fig. 1).

The three-year overall survival was comparable after autologous and allogeneic stem cell transplantation (50.0 vs. 53.8 %; $p = 0.52$, log-rank test) (Fig. 2). To address the role of allogeneic GvL-effects further in transplantation of T-cell lymphoma, the survival data were analysed according the transplant type (autologous vs. matched unrelated donor vs. matched related donor) and according the occurrence of GvHD vs. patients without any GvHD after stem cell transplantation. In the latter analysis patients after autoSCT or alloSCT not experiencing any GvHD were combined and compared to allografted patients with

Fig. 1 Overall survival

Fig. 2 Overall survival after autologous (auto) and allogeneic (allo) stem cell transplantation ($p = 0.52$, n. s., log rank test)

either acute or chronic GvHD. Patients after matched-related alloSCT had the best overall survival with 80 % after 4 years compared to 50.0 % after matched-unrelated alloSCT and 34.6 % after autoSCT ($p = 0.37$; log-rank test, curves not shown). The manifestation of acute or chronic GvHD did not influence the overall survival after SCT. The nine-year overall-survival was 38.9 % for both groups ($p = 0.84$; log-rank test) (Fig. 3).

A low or intermediate pre-transplant Sorrow-index compared to a higher score did not indicate a better survival. Stratification according the IPI (international prognostic index) revealed a tendency for better survival of patients with low/intermediate compared to those with higher risks (non-significant, data not shown).

Ten patients died within 2 years. Reasons for death were relapse ($n = 7$), EBV-PTL ($n = 2$) and sepsis ($n = 1$). The overall non-relapse mortality (NRM) was 15.0 % ($n = 3$) (Table 3). NRM after autoSCT and matched-related alloSCT was $n = 1$ and $n = 0$, respectively. Three patients

Fig. 3 Overall survival stratified for patients with any GvHD (either acute or chronic) or without, the latter including patients after autoSCT ($p = 0.84$, log-rank test)

Table 3 Patients' outcome after stem cell transplantation

Patient-#	Manifestation	SCT after salvage/primary therapy	Transplant type	Preparative regimen	Best result after SCT	Acute GvHD (stage)	Chronic GvHD	Relapse/progression?	OS (months)	Death (reason)
1	Extranodal	Salvage	Mud	RIC	CR	1–2	Extensive	Yes	6.0	Relapse
2	Nodal	Salvage	Mrd	MAC	CR	3	Limited	No	137.4	Alive
3	Nodal	Salvage	Mrd	MAC	CR	0	No	No	18.4	Alive
4	Nodal	Primary	Mud	RIC	CR	0	Limited	No	5.2	Alive
5	Extranodal	Salvage	Mud	RIC	CR	0	No	No	59.3	Alive
6	Extranodal	Salvage	Mrd	MAC	CR	2	No	No	17.5	Alive
7	Nodal	Salvage	Mrd	RIC	CR	0	No	Yes	0.8	Relapse
8	Extranodal	Salvage	Mud	MAC	CR	0	Limited	Yes	5.5	Relapse
9	Extranodal	Salvage	Mud	RIC	CR	1	No	Yes	2.5	EBV-PTL
10	Extranodal	Salvage	Mrd	RIC	CR	0	No	No	93.2	Alive
11	Extranodal	Salvage	Mud	MAC	CR	1	Extensive	No	16.2	EBV-PTL
12	Extranodal	Salvage	Mud	MAC	CR	0	No	No	5.0	Alive
13	Nodal	Salvage	Mud	MAC	CR	0	No	Yes	4.0	Relapse
14	Extranodal	Salvage	Mud	RIC	CR	3	No	No	8.1	Alive
15	Extranodal	Salvage	Autologous	HDT	CR	n.a.	n.a.	No	32.3	Alive
16	Extranodal	Primary	Autologous	HDT	PD	n.a.	n.a.	Yes	3.1	Relapse
17	Extranodal	Primary	Autologous	HDT	PD	n.a.	n.a.	Yes	4.7	Relapse
18	Nodal	Salvage	Autologous	HDT	CR	n.a.	n.a.	Yes	53.5	Relapse
19	Extranodal	Salvage	Autologous	HDT	CR	n.a.	n.a.	Yes	11.2	Sepsis
20	Extranodal	Salvage	Autologous	HDT	CR	n.a.	n.a.	No	11.4	Alive

See Table 2. *RIC* reduced-intense conditioning, *MAC* myeloablative conditioning

died from relapse or progress of the lymphoma after autoSCT and one patient after allo-sibling SCT. NRM after matched-unrelated alloSCT was 2/9 (22.2 %), both patients have died from EBV-PTL. Three patients died from underlying disease after unrelated alloSCT (Table 3). Donor lymphocyte infusions were given without success in one case with relapse and EBV-PTL, respectively.

Discussion

Conventional chemotherapy including anthracyclines leads to five-year overall survival rates of 30–40 % in the most common peripheral T-cell lymphoma entities [2, 3]. Relapsed or refractory PTCLs are considered incurable under conventional therapy [1, 3]. In consequence, different transplant approaches have been used as part of primary or salvage therapy of PTCL: high-dose therapy followed by autoSCT and allogeneic stem cell transplantation after myeloablative (MAC), reduced-intense (RIC) and minimal conditioning [4, 9, 21, 22]. However, in contrast to other haematological malignancies, no optimal strategy could be defined so far. In addition, there are hints for a role of graft-versus-lymphoma in therapy of PTCL, but the definite clarification is lacking [22].

The present investigation shows a 10 year survival of 39.5 % for patients with high-risk T-cell lymphoma after autologous or allogeneic stem cell transplantation. The stratification for transplant type revealed the best survival data (OS 80 % at 10 years) for familiar alloSCT compared to both other transplant modalities. These results are in line with reports from other investigators [5, 9, 23]. Corradini et al. [6] reported a 5 year overall survival of 80 % after RIC and alloSCT from mainly related donors. The overall survival of 59 % after minimal conditioning published by Shustov et al. [9] compared to the 80 % reported by Corradini might suggest a contribution of conditioning to outcome.

The results after autoSCT and unrelated alloSCT presented here are non-significant inferior compared to those after related alloSCT. In only two of six patients the autoSCT was part of the primary therapy, the other four patients were autografted in a salvage situation. Corradini et al. [5] reported a 10 year overall survival of 34 % after upfront autoSCT. The results published by Cairoli et al. [21] also support the concept of upfront autoSCT. Reimer et al. [24] described within a similar approach a 3 year overall survival rate of 48 %. The results after autoSCT seem to be better in patients with AITL. Kyriakou et al. [25] conducted a retrospective analysis in Europe and

described an overall survival of 67 % at 24 months. The same group could not state the superiority of alloSCT in AITL in a subsequent publication [26]. The literature gives no hints for a different outcome after related and unrelated alloSCT, since, in contrast to the present investigation, the vast majority of transplants reported by other investigators was conducted with grafts from sibling donors.

Graft-versus-leukaemia are mandatory for curing of several haematological malignancies by alloSCT [27, 28]. To elucidate this question for PTCL the patients were stratified into a group with any GvHD (acute and/or chronic) and patients without GvHD, including patients treated by autoSCT. Surprisingly no positive effect of any GvHD on survival was seen (Fig. 3). This observation is in contrast to those described by other investigators. Kanakry et al. [22] described an improved disease free survival in patients suffering from GvHD after alloSCT compared to those without GvHD. In a study by Okamura et al. [8] no relapses were seen after alloSCT for AITL in patients with chronic GvHD compared to 57 % in patients without GvHD and a better outcome for patients with acute GvHD was found compared to patients without, [26]. In addition, the 3-year overall survival of 59 % after minimal conditioning and the 10-year overall survival of 80 % after related alloSCT following MAC or RIC reported here supports a contribution of GvL-effects. The susceptibility of non-Hodgkin's lymphoma to GvL-effects has not been completely understood. Therefore the hypothesis could be raised, that only minimal GvL-effects are necessary for elimination of residual PTCL cells in contrast to other malignancies such as multiple myeloma [27]. No patient has died from GvHD in the presented investigation, however, basically could complications of manifest GvHD overbalance the GvL effects on minimal disease.

In conclusion, our data support the evidence that stem cell transplantation is a curative therapy even for advanced T-cell lymphomas. Furthermore, our study suggests a better outcome using a related donor compared to an unrelated donor. AutoSCT is an optional salvage strategy for patients without an allogeneic stem cell donor. A possible inferiority of unrelated alloSCT compared to related alloSCT should be object of further investigations.

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Conflict of interest No author has any competing interests.

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