Mature T- and natural killer (NK) cell neoplasms represent an extremely heterogeneous group of diseases with distinct epidemiologic, pathophysiological, immunophenotypic, molecular, and clinical features. First-line therapy may differ depending on the T-cell subtype but in many instances consists of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOP plus etoposide (CHOEP). Unfortunately, treatment results are often not satisfactory; patients with advanced disease and a high International Prognostic Index (IPI) especially progress during therapy or relapse frequently. A recent report from British Columbia demonstrated that survival of patients with relapsed T-cell lymphoma who do not receive an autologous or allogeneic transplant is dismal.

Describing treatment results without taking into consideration the differences as, for example, between anaplastic large cell lymphoma (ALCL) and NK/T-cell lymphoma is inadequate and can only be justified by the rarity of all T-cell lymphoma subtypes. The problem increases if rare disorders are treated with complex therapies like allogeneic transplantation of hematopoietic stem cells (alloSCT), which requires special expertise and consequently is used less frequently than indicated. Although numbers of alloSCTs in T-cell lymphoma have steadily increased during recent years, cases are still rare and reliable survival data for all T-cell subtypes are hard to find. In fact, most reports on alloSCT focus on the three most frequent subentities: ALCL, anaplastic lymphoma kinase (ALK)-negative angioimmunoblastic T-cell lymphoma (AITL), and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). With few exceptions ALCL has been excluded from recent reports on alloSCT because the prognosis of these patients is relatively good with conventional chemotherapy and the results of high-dose therapy and autologous stem cell transplantation (ASCT) seem reasonable in patients with relapsed ALCL. Other subentities like adult T-cell leukemia/lymphoma (ATLL), NK/T-cell lymphoma, hepatosplenic T-cell lymphoma, or cutaneous T-cell lymphoproliferative disorders are so rare and/or patient numbers reported have been so low, that reports focusing on these entities do not exist or suffer from very low patient numbers, making it difficult to judge the real impact of alloSCT. On the other hand, most publications on alloSCT for the more frequent T-cell lymphoma entities (ALK-negative ALCL, AITL, and PTCL) are “contaminated” by cases of these very rare subentities. It is also important to note that studies on alloSCT exclusively deal with patients transplanted for very advanced, often refractory disease.

Consequently, this review will focus on relapsed or refractory T-cell lymphoma, combining results of the most frequent T-cell subtypes. The few reports on some of the...
very rare T-cell subtypes, as well as the only published study in early disease, will also be reviewed.

**ALLOGENEIC TRANSPLANTATION IN RELAPSED AND REFRACTORY T-CELL LYMPHOMA**

The first report on alloSCT for relapsed and refractory T-cell lymphoma was published almost 10 years ago. Corradini et al described 17 patients with PTCL, AITL, or ALK-negative ALCL who had undergone alloSCT from an HLA-identical family donor (one unrelated donor) after reduced-intensity conditioning (RIC) with thiotepa, cyclophosphamide, and fludarabine. Prophylaxis of graft-versus-host disease (GvHD) consisted of cyclosporine A (CyA) and short-course methotrexate (MTX). The estimated 3-year overall survival (OS) and progression-free survival (PFS) rates were reported at 81% and 64%, respectively. More recently, the same group of investigators reported on 52 patients with all major T-cell subtypes, some of whom had been included in the previous report. In the new publication, the majority of patients still had an HLA-identical family donor (n = 33); only 13 donors were matched but unrelated and six donors were haploidential. The T-cell lymphoma subtypes were PTCL (n = 23), AITL (n = 9), ALK-negative ALCL (n = 11) and other histologies (n = 9). The median age of the patients was rather young (47 years); the same conditioning regimen as before was used, but anti-thymocyte globulin (ATG) was added for patients with an unrelated donor. The 5-year OS and PFS were reported at 50% and 40%, respectively, with no significant differences between the various histological subtypes. Of note, 51% of patients with chemosensitive disease but only 8% with chemoresistant disease were alive at the time of publication.

Older age (>45 years) was another factor negatively influencing OS. Relapse rates after RIC were high (49% at 5 years) but transplant-related mortality (TRM) was rather low (12%). Donor lymphocyte infusions (DLIs) were given to 12 patients for disease progression and eight of these (66%) had a response (five complete responses [CRs] and three partial responses [PRs]). The five CR patients were reported to be alive after a median observation time of 5 years (range, 2–8 years), while the PR patients all progressed and died.

Recently, the Center for International Blood and Marrow Transplant Research (CIBMTR) published an overview on their experience with autologous and allogeneic transplantation in patients with T-cell lymphoma. Covering the time period from 1996 to 2006 the analysis reported clinical results of 51 patients with ALCL (ALK status unknown), 63 patients with PTCL, NOS, and 12 patients with AITL. The median age of the recipients at the time of transplantation was 38 years (range, 5–60 years) and the median number of previous regimens was three. Sixty percent of recipients had an HLA-identical sibling donor, 24 patients had a matched unrelated donor, and 16 patients had a mismatched unrelated donor. For all 126 patients who had been allografted, PFS and OS at 3 years post-transplant were 36% and 39% after myeloablative conditioning and 33% and 52% after RIC. Results did not significantly differ for patients transplanted following myeloablative conditioning or RIC. Nonrelapse mortality (NRM) was 32% after myeloablative conditioning and 27% after RIC; relapse rates were 32% after myeloablative conditioning and 40% after RIC. There was no difference in outcomes between patients transplanted from HLA-identical siblings or matched unrelated donors. Neither acute nor chronic GvHD affected relapse or survival. Chemoresistant disease and higher number of chemotherapy lines before alloSCT had a negative impact on outcome.

Le Gouill et al summarized the experience of the SFGM (Société Française de Greffe de Moelle et Thérapie Cellulaire). Seventy-seven patients with a median age of only 38 years and various T-cell histologies (PTCL, n = 27; ALCL [five patients ALK-negative; eight ALK-positive; 13 with unknown ALK status]; AITL, n = 11; and other histologies, n = 12) were transplanted from mostly HLA-identical family donors (n = 60) or unrelated donors (n = 10). Seven patients received transplants from mismatched unrelated donors. The conditioning regimen was myeloablative in 57 of 77 patients (74%). With a median follow-up of 43 months, the 5-year OS and event-free survival (EFS) were 57% and 53%, respectively. Interestingly, two patients had received DLIs and achieved durable remissions afterwards. The 5-year TRM rate was 34%. Factors negatively influencing OS in multivariate analyses were grade 3–4 acute GvHD and chemoresistant disease at time of alloSCT. The only factor negatively influencing EFS was disease status.

Kyriakou et al reported the experience of the European Group for Blood and Marrow Transplantation (EBMT) in patients with AITL. Forty-five patients were transplanted between 1998 and 2005 from HLA-identical siblings (n = 26), matched unrelated donors (n = 16), or mismatched donors (n = 3). The median age of this group of patients was 48 years (range, 23–68); 33% of patients had failed a previous autograft. The conditioning regimen was total-body irradiation (TBI) and cyclophosphamide or etoposide in 16 patients; busulfan and cyclophosphamide or other chemotherapy in eight patients; and RIC regimens like fludarabine plus an alkylating agent or low-dose TBI (2 Gy) were used in 21 patients. GvHD prophylaxis was heterogeneous but mostly consisted of CyA alone, CyA plus methotrexate, or CyA plus mycophenolate mofetil (MMF). The NRM was 25% at 1 year after transplantation, the relapse rate was estimated at 20% at 3 years, PFS was 54%, and OS was 64% at 3 years after transplantation. Again, patients with chemosensitive disease had a significantly better OS than patients with refractory disease (81% vs 37% at 3 years). Interestingly, none of the 19 patients...
developing chronic GvHD relapsed after transplantation, whereas 57% of patients (n = 15) not developing chronic GvHD relapsed. Two of four patients experiencing relapse after alloSCT responded to DLI.

Glass et al reported on 63 patients with PTCL (n = 25), AITL (n = 12), ALK-negative ALCL (n = 11), T-lymphoblastic lymphoma (n = 6), and T-lymphoproliferative leukemia (T-PLL) (n = 5), who received an alloSCT from an HLA-identical sibling (n = 22), a matched unrelated donor (at least HLA 8/8 loci compatible, n = 41), after conditioning with fludarabine (125 mg/m²), busulfan (12 mg/kg), and cyclophosphamide (120 mg/kg body weight). GvHD prophylaxis consisted of MMF and tacrolimus. In contrast to other reports, 53% of patients had active disease immediately prior to transplantation. OS at 3 years was 42% and PFS was 43%. TRM was 32.1% and the relapse rate was 35% for the whole group of patients. No significant differences in outcome for the different histologies were seen; only the IPI before transplantation significantly influenced treatment results. Patients with CR, PR, or stable disease prior to alloSCT had very similar outcomes, while patients with progressive disease fared less well. Patients with acute GvHD grade >2 showed better results than patients with no GvHD or GvHD grade 1.

Wulf et al (manuscript in preparation) recently updated the German results in a larger cohort of 97 patients and confirmed the aforementioned results. Obviously, conditioning with fludarabine, busulfan, and cyclophosphamide followed by transplantation of matched (10/10) related or unrelated grafts can overcome chemo-resistance in a sizable fraction of patients. GvHD prophylaxis without ATG led to frequent and severe acute GvHD and high TRM. Consequently, our next study will include ATG into the conditioning regimen for all patients.

Jacobsen et al examined 52 adult patients who underwent allogeneic transplantation at the Dana-Faber Cancer Institute between 1997 and 2009. The T-cell histologies varied broadly but most patients suffered from PTCL (38%), mycosis fungoides (MF)/Sezary syndrome (SS) (13%), ALCL (12%), or AITL (10%). The median age of the patients was 46 years, and only 21% of patients had failed a previous autograft. TRM at 3 years was 27% (36% for patients after myeloablative conditioning and 14% after RIC). The cumulative incidence of relapse at 3 years was 43% (33% with myeloablative and 57% with RIC [P = .049]). OS at 3 years was 41% and PFS was 30%. In multivariable competing risks regression analysis of NRM and relapse, RIC was a significant factor for relapse (P = .00005), and conditioning intensity was not associated with NRM. Interestingly, nine patients received DLI after relapse. Five of these nine patients were still alive at the time of this report and the median OS had not been reached.

Delioukina et al reported on 27 patients treated with alloSCT after RIC with fludarabine and melphalan. Median age of patients was 50 years and 56% of patients had an HLA-identical sibling donor. Eleven of these patients (41%) suffered from a cutaneous T-cell lymphoma. The 2-year-probability of OS was 55%; PFS was 47%. The cumulative incidence of relapse/progression was 30% and NRM was 22%.

Czajczynska et al recently reported the single-center experience of the University of Kiel, Germany. Twenty-four patients with a median age of 53 years and all subtypes of T-cell lymphomas received standardized salvage therapy followed by BEAM (BCNU, etoposide, cytosine arabinoside, melphalan) chemotherapy together with alemtuzumab for conditioning. The donors were matched and unrelated in the majority of cases. Six patients (25%) died of NRM, and six patients relapsed. Twenty of 22 evaluable patients reached CR after alloSCT, and 50% of patients were alive and in CR at last follow-up. The OS at 3 years was reported at 42% (Table 1).

### Table 1. Results of Allogeneic Transplantation in Relapsed/Refractory T-Cell Lymphomas

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>No. of Patients</th>
<th>Conditioning</th>
<th>NRM</th>
<th>REL</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodero (2011)⁹</td>
<td>52</td>
<td>TT/Cy/Flu</td>
<td>12%</td>
<td>49%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Le Gouill (2008)¹⁰</td>
<td>77</td>
<td>Myeloablative</td>
<td>34%</td>
<td>N.E.</td>
<td>N.E.</td>
<td>57%</td>
</tr>
<tr>
<td>Kyriakou (2009)¹¹</td>
<td>45</td>
<td>Various</td>
<td>25%</td>
<td>20%</td>
<td>20%</td>
<td>64%</td>
</tr>
<tr>
<td>Glass (2011)¹²</td>
<td>63</td>
<td>Flu/Bu/Cy</td>
<td>32%</td>
<td>43%</td>
<td>42%</td>
<td>97%</td>
</tr>
<tr>
<td>Jacobsen (2011)¹⁴</td>
<td>52</td>
<td>TBI/Cy</td>
<td>36%</td>
<td>33%</td>
<td>30%</td>
<td>41%</td>
</tr>
<tr>
<td>Delioukina (2012)⁵</td>
<td>27</td>
<td>Bu/Flu</td>
<td>14%</td>
<td>57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czajczynska (2013)¹⁶</td>
<td>24</td>
<td>BEAM/ALEMT</td>
<td>25%</td>
<td>25%</td>
<td>N.E.</td>
<td>42%</td>
</tr>
<tr>
<td>Smith (2013)⁹</td>
<td>74</td>
<td>MAC</td>
<td>32%</td>
<td>32%</td>
<td>36%</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>RIC</td>
<td>27%</td>
<td>40%</td>
<td>33%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Abbreviations: NRM, non-relapse mortality; REL, relapse; PFS, progression-free survival; OS, overall survival; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; TT, thiopeta, cyclophosphamide, fludarabine; Flu, fludarabine; BU, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; Mel, melphalan; BEAM/Alemt, BCNU, etoposide, cytosine arabinoside, melphalan, alemtuzumab.
ALLOGENEIC TRANSPLANTATION AS PART OF FIRST-LINE THERAPY IN T-CELL LYMPHOMA

The poor prognosis of most patients with T-cell lymphoma after conventional chemotherapy and the favorable results of alloSCT in patients with relapsed and refractory T-cell lymphoma raised interest in using alloSCT earlier in the course of diseases. Recently, Corradini et al reported the first results of a prospective study following such an approach.17 The investigators enrolled 64 patients, mostly with PTCL, NOS (n = 38) on a study that commenced treatment with two courses of CHOP-21 preceded by alemtuzumab (30 mg total dose). Treatment continued with two courses of Hyper-C-Hidam (high-dose methotrexate, hyperfractionated cyclophosphamide, and high-dose cytosine arabinoside). Responding patients were to receive an autologous or an allogeneic graft based on donor availability (genetic randomization).

Disappointingly, only 62% of patients finally received a transplant; the other patients had either died of toxicity (five patients) or suffered an early relapse (18 patients) before proceeding to transplantation. The conditioning regimen again consisted of thiotapecyclophosphamide, and fludarabine. Sixteen patients (70%) who received an alloSCT were alive in CR at the time of the report, four patients had died of disease, and three died of toxicity. The investigators concluded that the use of alemtuzumab and pretransplant high-dose chemotherapy was unable to increase the number of patients proceeding to transplantation. Because of low patient numbers, a statistically sound comparison of alloSCT and high-dose chemotherapy/AcT was not possible; however, no obvious differences in OS of patients receiving autologous or allogeneic transplantation was noted.

ALLOGENEIC TRANSPLANTATION FOR PATIENTS WITH MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

After a number of case reports had documented the feasibility and had reported promising results,18 the EBMT published the largest series of patients with MF or SS who had received an allogeneic transplant for relapsed or refractory disease.19 A total of 60 patients with MF (n = 36) or SS (n = 24) received a first allogeneic transplant from matched related (n = 45) or unrelated (n = 15) donors. The median patient age was 46.5 years, and 40 patients presented with advanced stage at the time of transplantation. Forty-four patients had been prepared with RIC and 16 patients with myeloablative conditioning. Twenty-five patients underwent T-cell depletion, 20 of them using alemtuzumab. The estimated OS and PFS at 3 years were 54% and 34%, respectively. Advanced disease and the use of an unrelated donor negatively influenced treatment results. NRM was 22% at 2 years; myeloablative conditioning and poor performance status had independent adverse effects on NRM. The cumulative incidence of relapse was 47% at 3 years. T-cell depletion was the strongest adverse factor influencing relapse rates. Chemosensitivity was not associated with the risk of relapse. These results have recently been updated.20 With a median follow-up of 5 years, OS and PFS are reported at 48% and 33%, respectively. Disease progression remains the major problem, with 26 patients having relapsed or progressed at a median of 3.8 months. Advanced disease, having an unrelated donor, and the use of myeloablative conditioning had a negative impact on survival.

ALLOGENEIC TRANSPLANTATION IN PATIENTS WITH NK/T-CELL LYMPHOMA

NK/T-cell lymphoma is a very rare disease with a highly skewed geographical distribution. Most cases are reported from Asia and South America; cases from other areas are very rare. Except for patients with localized disease restricted to the nasal cavity, NK/T-cell lymphoma carries a very poor prognosis. The recent use of MTX- and 1-asparaginase–containing regimens have improved outcome.21,22

A report from Japan summarized the investigators’ experience in 28 patients with NK cell neoplasms (22 extranodal NK/T-cell lymphomas, three blastic NK-cell lymphomas, and three aggressive NK cell leukemias). Twenty-two patients had matched related donors; conditioning was myeloablative in 23 patients. At 2 years, PFS and OS were 34% and 40%, respectively.23

ALLOGENEIC TRANSPLANTATION IN PATIENTS WITH ADULT T-CELL LEUKEMIA/LYMPHOMA

Almost all reports on alloSCT for adult T-cell leukemia/lymphoma (ATLL) come from Asian countries and reflect the geographical distribution of this disease.24 By far the largest study on patients with adult T-cell leukemia, including patients with the lymphomatous subtype, was published by investigators from Japan.25 A total of 386 patients received HLA-matched, related bone marrow or peripheral blood stem cells (n = 154), mismatched related bone marrow stem cells or peripheral blood stem cells (n = 43) or unrelated bone marrow stem cells (n = 99). Ninety patients received cord blood.

The 3-year OS for the entire cohort was 33%. Multivariable analysis revealed four factors associated with lower survival: age >50 years, male sex, response status other than CR, and use of cord blood compared with HLA-matched related grafts. TRM was rather high (37% at 3 years). Patients with a human T-lymphotropic virus (HTLV)-1–seropositive donor had a higher risk of relapse after transplantation: 18 of 48 patients (38%) who had an HTLV-1–positive donor relapsed after transplantation in contrast to 16 of 65 patients (25%) with an HTLV-1–negative donor. The investigators concluded that alloSCT is an effective treatment in selected patients with ATLL in
particular if the extremely poor prognosis of such patients with any other treatment modality is considered.

ALLOGENEIC TRANSPLANTATION IN HEPATOSPLENIC T-CELL LYMPHOMA

So far only case reports of patients transplanted for alpha/beta or gamma/delta hepatosplenic T-cell lymphoma exist. These reports do not allow conveying a clear picture of how successful alloSCT in patients with hepatosplenic T-cell lymphoma might be. Clearly, one major problem for many patients is that the rapid progression of the underlying disorder does not allow finding a suitable donor and proceeding to transplantation on time. An EBMT project which at this time is ongoing identified not more than 20–25 patients who had been allografted for hepatosplenic T-cell lymphoma, confirming the rarity of the disease and the difficulty in bringing such patients to transplant.

CONCLUSIONS

In patients with relapsed and refractory mature NK and T-cell lymphomas, allogeneic transplantation of hematopoietic stem cells results in 35%-50% of patients remaining alive and free of disease at follow-up periods of 3–5 years. With one exception, these results were obtained in patients suffering from relapsed or refractory disease, and regardless of whether RIC or myeloablative conditioning and HLA-matched family or unrelated donors were used. As with other diseases, RIC might have advantages over myeloablative conditioning in older and unfit patients and results of alloSCT tend to be less favorable if other than HLA-matched donors need to be used.

No other treatment modality including the new drugs or autologous transplantation resulted in such favorable outcomes. One major problem that ASCT and alloSCT have in common is the tendency of patients with T-cell lymphoma to progress during treatment or relapse early after end of therapy. Therefore, about one third of patients scheduled for transplantation will never be transplanted. In this situation new drugs or drug combinations may be extremely helpful to facilitate transplantation in more patients. Likewise, these drugs may have the potential to induce further remissions after relapse following alloSCT.

The relatively low relapse rates after alloSCT as well as the high efficacy of DLLIs in patients relapsing after alloSCT demonstrate the existence of a graft–versus–T-cell lymphoma effect. Next-generation studies will have to modify details of the transplant procedure to reduce NRM, lower relapse rates, and improve PFS and OS.

A current study run by the German High Grade Lymphoma Study Group (DSHNHL) in cooperation with the French LYSA (Lymphoma Study Association) hopefully will define the role of alloSCT as part of first-line therapy for mature T-cell lymphoma.

REFERENCES


