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Anti-Tumour Treatment

The role of high dose chemotherapy and autologous stem-cell transplantation in peripheral T-cell lymphoma: A review of the literature and new perspectives

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ABSTRACT

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of non-Hodgkin's lymphoma that carries, except for ALK-positive anaplastic large cell lymphoma, a poor prognosis. Only a third of patients live 5 years past diagnosis. The incidence of PTCL has been increasing during the last two decades. In recent years, there was a rising interest in PTCL manifested by the abundance of publications dedicated exclusively to this disease. The international T-cell lymphoma project was formed with an aim of unifying efforts towards a better understanding of the diagnosis and management of this disease. Given the poor outcomes of PTCL patients, high-dose chemotherapy and autologous stem-cell transplantation (HDT/ASCT) have been used in the up-front and salvage settings, with different success rates. However, there are no prospective randomized controlled trials addressing the role of HDT/ASCT in a PTCL-restricted population. This article critically reviews the data available from the retrospective and prospective studies addressing this topic. We will emphasize the favorable prognostic factors of HDT/ASCT such as a solid remission at the time of transplantation, a chemotherapy sensitive disease and a low prognostic index score. As novel agents and new therapeutic strategies are introduced, there is a continued need for prospective randomized trials to define the optimal use of HDT/ASCT in managing PTCL.

Introduction

In 2012, an estimated 70,130 cases of non-Hodgkin's lymphoma (NHL) will be diagnosed and 18,940 patients with NHL will die in the United States.[1] Five to 20% of NHL is categorized as peripheral T-cell lymphoma (PTCL).[2] This number is the highest in Asia where PTCL accounts for 15–20% of all lymphomas.[3,4] The most common subtypes are PTCL-not otherwise specified (PTCL-NOS) (25.9%), angioimmunoblastic T-cell lymphoma (AITL) (18.5%), anaplastic large-cell lymphoma (ALCL) (12.1%), and natural killer/T-cell lymphoma (NKTCL) (10.4%).[5,6] The incidence of PTCL is rising with nearly 3 times more cases diagnosed in the US in 2005 than in 1992.[7] Except for ALCL, ALK positive (ALK$^+$ALCL), hepatosplenic lymphoma (HSL), and nasal NKTCL, PTCL patients are of old age (>60 years),[5] and present with advanced stage.[5] PTCL, with the exception of ALK$^+$ALCL[8] and primary cutaneous ALCL, carries universally a poor outcome comparing to B-cell lymphomas (BCL).[5,9–12] The international T-cell lymphoma (TCL) project found that patients with PTCL-NOS have a 5-year overall survival (OS) and failure free survival (FFS) of only 32% and 20%, respectively.[6] This is probably due to the poor prognosis of T-cell immunophenotype[13] and to advanced adverse prognostic factors. The international prognosis index (IPI) and the prognostic index for PTCL (PIT)[14] are used to stratify patients into risk groups. Additional factors including thrombocytopenia, bulky disease, the number of transformed tumor cells (>70%), elevated Ki-67, over-expression of p-53, expression of BCL-2 and other are poor prognosticators in PTCL.[6,15–17] Historically, PTCL was treated like aggressive BCL, with an anthracycline-based combination chemotherapy including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with disappointing results[5]; a comprehensive meta-analysis confirmed this poor outcome, reporting a 5-year OS of 37%.[12] There are no randomized controlled prospective studies comparing the treatment strategies dedicated exclusively to PTCL. Thus, today, the National Comprehensive Cancer Network (NCCN) guidelines recommend treating patients with non-ALK$^+$ALCL PTCL on a clinical trial. Several groups around the world suggest that high dose chemotherapy and autologous stem cell transplantation (HDT/ASCT) in the front-line setting or in relapsed disease, is beneficial for PTCL patients. The first report comparing the outcomes of patients with relapsed TCL and those with relapsed BCL was published in 1990, with encouraging results.[18] In most guidelines, HDT/SCT is listed as an option for consolidation after induction therapy in non-ALK$^+$ALCL PTCL patients who achieve a complete response (CR) or partial response (PR), and in relapsed disease for appropriate candidates.

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Here, we review and comment on the entire body of prospective and retrospective data, from the last 20 years, on HDT/ASCT in PTCL, and give new perspective on the future of HDT/ASCT in the light of the novel therapy.

Autologous stem-cell transplantation in PTCL

Randomized prospective trials (RCT)

So far, there are no RCT exclusively dedicated for PTCL assessing the role of HDT/ASCT in the front-line or relapsed settings of PTCL patients. Only the GELA (Group d'Etude des Lymphomes de l'Adulte) from France published the results of two randomized prospective trials on the role of up-front HDT/ASCT in aggressive NHL including TCL (Table 1). A total of 451 patients with intermediate/high- and high-risk (2 and 3) prognostic factors identified by age-adjusted IPI (aa-IPI) were included in the LNH 87-2 trial; 17% had T-cell phenotype. Patients achieving CR after induction chemotherapy were randomized to consolidation sequential chemotherapy or HDT/ASCT; the authors conclude that HDT/ASCT benefits these patients; shortcomings of this trial are that only 277 out of 451 enrolled patients achieved CR and were randomized.[19,20] The second trial, LNH 93-3, enrolled 370 patients with poor prognosis aggressive NHL; 22.7% had PTCL. The investigators compared sequential consolidation chemotherapy to a shortened treatment followed by HDT/ASCT. This trial reported an inferior outcome for patients in the HDT/ASCT arm compared to those in the chemotherapy arm. T-cell phenotype was an independent prognosticator of worse survival ($p = 0.009$).[21]

Later, the data from both trials was pooled and each NHL subtype was matched with a control group to assess the therapeutic effect of HDT/ASCT among different histologies. This analysis failed to prove any benefit of up-front HDT/ASCT in PTCL.[22] Nevertheless, only a minority of the transplanted patients had TCL ($n = 52$) including those with ALK$^+$ALCL and precursor TCL, which make the interpretation of these results difficult.

Prospective trials

To date, there are six prospective trials addressing the role of HDT/ASCT in the frontline treatment of PTCL (Table 1).

The largest is the multicentric NGL-T-01 study from the Nordic lymphoma group (NGL).[23] The investigators evaluated 160 patients with PTCL, appropriately excluding ALK$^+$ALCL; most patients had advanced-stage disease (81%). Patients were induced with a dose-dense chemotherapy consisting of CHOP-Etoposide (CHOEP). Of the 114 patients (71%) who underwent HDT (BEAM or BEAC)/ASCT, 90 were in CR at 3 months post-transplant. In an intent-to-treat analysis, and after a median follow-up of 60 months, 83 patients were still alive, the 5-year OS and PFS for the entire cohort were 51% and 44% respectively. ALCL, ALK negative (ALK$^-$ALCL) did particularly well with 5-year OS and PFS of 70% and 61% respectively. This data is not is not published yet; it was first presented at the 2009 European Hematology Association (EHA)[24] and recently updated at the 2011 American Society of Hematology (ASH) annual meeting.[23] The NGL reported at the 2010 ASH annual meeting the favorable results of the ALK$^-$ALCL and the Enteropathy-Associated T-cell lymphoma (EATCL) subgroups of the NGL-T-01. In the former subgroup, 24/31 patients with ALK$^-$ALCL (19% of the study population) achieved CR/PR and underwent HDT/ASCT; only 6 patients relapsed after ASCT. The 3-year OS and PFS were impressive, 73% and 64% respectively, with the survival curve suggesting a plateau.[25] In the latter subgroup, the authors analyzed the outcome of EATCL, which is historically known to carry poor prognosis when treated only with conventional chemotherapy. NGL-T-01 included 21 patients with EATCL (13%); after induction, 14 patients (67%) achieved CR/unconfirmed CR (CRu) and had HDT/ASCT. Six patients relapsed as well after the transplant; the 3-year OS and PFS were 45% and 40% respectively.[26]

The second largest study is the multicentric trial from Germany by Reimer et al.[27] Eighty-three patients with non-ALK$^+$ALCL PTCL were enrolled. Induction was 4–6 cycles of CHOP chemotherapy; the myeloablative conditioning consisted of cyclophosphamide and total body irradiation (TBI). Patients achieving CR or PR went onto transplant. Only 55/83 (66%) of the patients received HDT/ASCT. The remaining 28 (34%) patients did not get transplantation, mainly due to progressive disease (PD). With a median follow-up of 33 months, 43 patients were still alive. In an intent-to-treat analysis, the overall response rate (ORR) was 66% (58% CR and 8% PR), and the 3-year OS and PFS were 48% and 36% respectively. These results were considerably lower to what the Nordic group reported. Most of the patients in this study had stage 3 or 4 disease (75%) and intermediate or high aaIPI (85.5%). In univariate analysis, a high PIT score was significantly associated with worse OS ($p = 0.0414$), and intermediate/high and high IPI showed a nonsignificant trend for a shorter OS. Interestingly, CR showed also only a non-significant trend for longer OS.

The Italian group published the long-term results of 2 prospective phase II multicentric studies investigating the role of front-line HDT/ASCT in 62 patients with advanced stage PTCL.[28] ALK$^+$ALCL patients constituted 30% of the study population. Patients in the first study were induced with doxorubicin, vincristine and prednisone (APO) followed by a combination of dexamethasone, high dose cytarabine and cisplatin (DHAP). In the second study, the patients ($n = 30$) received a combination of methotrexate, adriamycin, cyclophosphamide, oncovin and prednisone (MACOP-B) followed by mitoxantrone and cytarabine. BEAM chemotherapy was given to 46/62 (74%) patients followed by ASCT. Sixteen (26%) patients did not proceed to HDT/ASCT due to PD. This study had the advantage of a long median follow-up time of over 6 years (73 months). In an intent-to-treat-analysis, the 12-year OS, DFS and EFS were 34%, 55% and 30% respectively. A separate analysis of ALK$^+$ALCL patients showed an expected significantly better 12-year OS and EFS (62% and 54% respectively) than those for the other non ALK$^+$ALCL PTCL patients (21% and 18% respectively). In univariate analysis, intermediate and high aaIPI (2–3) were associated with a shorter 10-year EFS of 25% compared to 48% for low IPI (0–1). In contrast to the German prospective study,[27] and in multivariate analysis, achieving a CR prior to transplant was strongly correlated with a superior 10-year EFS and OS compared to less than a CR (EFS of 47% vs. 11% and OS of 48% vs. 22% respectively; $p < 0.001$ for both).

The Korean group reported at the 2011 ASH annual meeting the results of a multicenter phase 2 trial of frontline ASCT in patients with non- ALK$^+$ALCL PTCL.[29] Of the 46 patients enrolled in this study, only 31 patients were transplanted. The majority of the patients were classified as high-intermediate or high risk by the aaIPI or PIT scores. The induction was CHOP, CHOP-like or non-anthracycline-based chemotherapy. The conditioning regimen consisted of busulfan, cyclophosphamide and etoposide. Twenty-three and eight patients were in CR and PR respectively before transplantation. Six of the eight patients in PR at pretransplantation improved to CR after HDT/ASCT. After a median follow-up of 33 months, 50% of the patients were still alive. In an intent-to-treat analysis, the 5-year PFS and OS were 47% and 48% respectively. However, the transplanted patients had an improved 5-year PFS and OS of 55% and 57% respectively.

The CELCAB group from Spain reported a study that did not find a clear benefit for HDT/ASCT in first-line treatment of PTCL.[30] Here, 41 patients with non ALK$^+$ALCL PTCL were enrolled and received 3 courses of high-dose CHOP (cyclophosphamide 2 g/m^2, doxorubicin