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A Review of Cellular Therapies for Chronic Lymphocytic Leukemia

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia, accounting for 25% to 30% of all leukemia in the Western world. Generally, CLL is considered incurable—although readily controllable—with combination therapies, including purine analogues, monoclonal antibodies, and newer targeted agents, such as ibrutinib [1]. Furthermore, heterogeneous outcomes result from different prognostic features at diagnosis or during evolution of disease. However, long-term disease-free survival (DFS) is increasingly possible with hematopoietic cell transplantation (HCT). This review will synthesize the data demonstrating lack of overall survival benefit for autologous HCT, provide outcomes for allogeneic HCT, and discuss novel cellular approaches in development to further decrease relapse risk.

AUTOLOGOUS HCT

Autologous HCT was initially reported in management of CLL in 1993, and a retrospective analysis published in 2004 documented improved overall survival (OS) for patients with unmutated immunoglobulin variable region heavy chain (IGVH) [2]. Since that time, several analyses, including randomized controlled trials, have demonstrated an improved event-free survival (EFS) with autologous HCT as consolidation for first or second remission; however, no benefit in OS is noted [3-6]. The three randomized trials all used what is now considered to be suboptimal initial therapy, before the development of combination chemotherapy with fludarabine, cyclophosphamide (CY), and rituximab (FCR) as the standard of care [7].

In 2011, the Société Française de Greffe de Moelle et de Thérapie Cellulaire and Groupe Français d'étude de la Leucémie Lymphoïd Chronique reported the results of their randomized phase 3 trial for initial therapy [4]. The trial enrolled 241 patients between 2001 and 2007. Patients received initial therapy with mini-CHOP (CY, adriamycin, vincristine, and prednisone) for 3 courses followed by 3 courses of fludarabine. The overall response rate to induction was 88.3% (complete remission [CR], 44.6%; partial remission [PR], 43.7%). Patients in PR received further therapy with 1 or 2 cycles of DHAP (cisplatinum, cytarabine, and dexamethasone). Patients were then randomized to receive an unmanipulated autologous stem cell graft after CY and total body irradiation (TBI) versus observation if in CR or versus fludarabine and CY for 3 cycles if only in PR before treatment with DHAP. Of patients randomized to autologous HCT, 27 (27.6%) did not receive assigned therapy (CR, 15 of 52; PR 12 of 46). Outcomes were affected by disease status after induction. Patients in CR and assigned to autologous HCT had 79.8% (95% confidence interval [CI], 69% to 92%) EFS at 3 years, compared with 35.4% (95% CI, 24% to 54%) in the observation arm. Patients in PR had no improvement in EFS after autologous HCT (HCT, 48.9% [95% CI, 35% to 68%]; fludarabine and CY, 44.4% [95% CI, 32% to 62%]). Even though HCT more than a doubled EFS for CR patients, OS was not prolonged (HCT, 95.7% [95% CI, 90% to 100%]; observation, 97.8% [95% CI, 94% to 100%]), suggesting that salvage treatment after relapse is effective.

The European Blood and Marrow Transplant Group (EBMT) reported the results of their randomized trial comparing autologous HCT (n = 112) to observation (n = 111) after first or second line therapy for patients with CLL [3]. In this trial, induction therapy was not specified, but patients were eligible for randomization only if they were in CR, nodular PR, or very good PR. More than 80% of patients enrolled after first-line therapy (HCT, n = 92; observation, n = 92) and 82 (73%) HCT patients and 83 (75%) observation patients received at least 3 cycles of fludarabine before randomization. Notably, only 3 patients, all randomized to observation, received FCR. All patients were mobilized with either CY or Dexa-BEAM (carmustine, etoposide, cytarabine, melphalan), and cells were cryopreserved for future use in patients randomized to observation. Patients received conditioning with either CY/TBI or BEAM. Similar to the results of the Société Française de Greffe de Moelle et de Thérapie Cellulaire/Groupe Français d'étude de la Leucémie Lymphoïd Chronique trial, 5-year EFS was almost doubled after autologous HCT (HCT, 42%; observation, 24%; hazard ratio, .44

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[95% CI, .3 to .65]) but did not translate to an improved OS (HCT, 85.5% [95% CI, 77% to 94%]; observation, 84.3% [95% CI, 75% to 93%]). The presence of 17p deletion or 11q deletion was associated with 3.6-fold (95% CI, 2.05 to 6.31) greater risk of death or progression.

More recently, the Groupe Ouest Est d'Etude des Leucémies et autres Maladies du Sang reported the final results of the LLC 98 trial that enrolled patients (n = 86) between 1999 and 2004 with a median follow-up of 77.1 months [5]. Patients randomized to chemotherapy received CHOP for 6 courses (n = 39) followed by either CHOP every 3 months for 6 additional cycles for patients with CR or PR or 3 to 6 cycles of fludarabine if less than a PR after CHOP. Those randomized to autologous HCT (n = 43) received 3 cycles of CHOP followed by CY mobilization (for those patients in CR or very good PR) or 1 to 3 cycles of fludarabine (for those patients in PR) and then CY mobilization.

Autologous HCT patients received CY/TBI conditioning and a CD34-selected graft. This trial closed early due to concerns regarding the lower efficacy of chemotherapy with CHOP as compared to fludarabine. Additionally, only 29 patients (67.4%) received autologous HCT as assigned. Despite these limitations, patients randomized to autologous HCT had a median progression-free survival (PFS) of 53.1 months (95% CI, 40.3 to 65.9) compared with only 22 months (95% CI, 12.6 to 31.3) for the maintenance arm. Once again, OS was not affected with median survival after autologous HCT of 107.4 months (95% CI, 58.2 to 156.6) compared with 104.7 months (95% CI, 99.9 to 109.5) after maintenance therapy.

As previously noted, nearly all patients in these trials received what is now considered less than optimal front-line induction therapy, and it is unclear whether the results of these trials would differ if the current standard of FCR had been used or whether HCT after induction with FCR could improve OS. In an attempt to assess the impact of autologous HCT compared with FCR alone, the German CLL group conducted a retrospective cohort analysis comparing subsets of patients treated on the CLL3 trial and the CLL8 trial [6,7]. Patients enrolled in the phase 2 CLL3 trial received induction therapy with CHOP (n = 93) or fludarabine (n = 14) or fludarabine/CY (n = 54) for a median of 3 (range, 1 to 6) courses followed by Dexa-BEAM for mobilization (n = 156), and then autologous HCT (n = 131) with a B cell–depleted graft after CY/TBI conditioning. For this cohort comparison, patients were included (CLL3, n = 110; CLL8 [FCR], n = 126) if they were untreated, 60 years of age or younger, and had fluorescein in situ hybridization (FISH) and IGVH mutational analyses completed. Once again, PFS was improved with autologous HCT (median, 6.2 years) compared with chemotherapy alone (median, 4.3 years) but without improved OS at 4 years (HCT, 86% [95% CI, 80% to 93%]; FCR, 90% [95% CI, 84% to 95%]).

In summary, autologous HCT in first remission improves DFS but does not yet improve OS. Consequently, autologous HCT should not be considered outside of a clinical trial, ideally investigating novel approaches to prevent relapse.

ALLOGENEIC HCT

Allogeneic HCT harnesses both the anticancer effects of the conditioning regimen as well as the graft-versus-tumor effects of the donor immune system. This potentially results in long-term DFS (ie, cure) for some patients with CLL [8]. However, the toxicity and prolonged sequelae of allogeneic HCT and the generally older age of CLL patients has limited this approach. The EBMT Consensus criteria recommends allogeneic HCT for younger patients with nonresponse or relapse less than 12 months from purine analogue therapy; relapse at less than 24 months from purine analogue combination therapy or autologous HCT; and in patients with 17p abnormalities [9]. Several analyses (Table 1) published recently highlight the improved outcomes and applicability for this approach using reduced-intensity conditioning (RIC) [10-15].

Sorror et al. reported outcomes for 82 patients with fludarabine refractory CLL who received nonmyeloablative conditioning with TBI 200 cGy ± fludarabine followed by related (n = 52) or unrelated (n = 30) allogeneic HCT [12]. At the time of HCT, 78 patients (95%) had measurable disease, and the overall response rate was 70% (CR, 55%; PR, 15%). In this series, the 5-year outcomes for OS, PFS, non-relapse mortality (NRM), and relapse were 50%, 39%, 23%, and 38% respectively. These outcomes are similar to those reported by the MD Anderson Cancer Center group [13]. In this study, 86 patients with relapsed/refractory CLL received RIC conditioning followed by either matched sibling (n = 43) or unrelated (n = 43) HCT. Nearly all patients (90.6%) received conditioning with fludarabine, CY, and high-dose rituximab with tacrolimus and mini-methotrexate for graft-versus-host disease (GVHD) prophylaxis. After HCT, 43 patients had persistent or recurrent disease that was managed with either rituximab, withdrawal of immune suppression, or donor lymphocyte infusion. After these measures, 20 (47%) patients had a CR, indicating a graft-versus-CLL effect. Overall, 5-year PFS and OS were 36% (95% CI, 25% to 46%) and 51% (95% CI, 39% to 62%) respectively. More recently, Kharfan et al. reported results of a novel reduced-toxicity conditioning regimen with pentostatin, i.v. busulfan, and rituximab [16]. Nineteen (45%) of 42 patients had CLL;17 (89%) with residual disease at time of HCT. After HCT, 10 (53%) of the CLL patients had a CR, including 2 patients with stable or progressive disease at transplantation. An additional 5 (28%) of the CLL patients obtained a PR compared with disease status before HCT. At 2 years, the PFS and OS for the 19 CLL patients were 55% (95% CI, 32% to 78%) and 66% (95% CI, 43% to 86%), respectively. GVHD remains a barrier to successful allogeneic HCT because of its contribution to NRM and its impact on quality of life. In these studies, the risks of acute GVHD grade II to IV ranged from a low of 37% (95% CI, 27% to 47%) to a high of 59% (95% CI, 43% to 75%) [12,13,16]. Chronic GVHD, categorized as extensive or moderate/severe, occurred in 49% to 58% of patients.

Various prognostic factors affect treatment responses in patients with CLL. It appears, however, that allogeneic HCT can overcome certain factors, including overexpression of ZAP-70, 17p deletion, and in some cases, Richter's transformation [11,17,18]. For example, an analysis of 25 patients with ZAP-70 overexpression and 13 patients without ZAP-70 overexpression at MD Anderson showed no statistically significant association with disease progression after HCT [17]. The EBMT analyzed 44 patients with 17p deletion who received primarily (89%) RIC allogeneic HCT between 1995 and 2006 [11]. Overall survival at 3 years was 44% (95% CI, 28% to 60%) and PFS was 37% (95% CI, 22% to 52%), and no relapses were observed beyond 4 years in this high-risk group of patients. Assessments of both autologous and allogeneic HCT for patients with Richter's transformation have been recently reported as well [18]. For the 25 patients receiving RIC allogeneic HCT, OS at 3 years was 36% (95% CI, 14% to 57%). Additional prognostic features that portend an