Experimental Hematology

Experimental Hematology 2016;44:3–13

Induction chemotherapy followed by up-front autologous stem cell transplantation may have a survival benefit in high-risk diffuse large B-cell lymphoma patients

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(Received 14 April 2015; revised 5 July 2015; accepted 17 August 2015)

We compared the outcomes of patients with higher-risk diffuse large B-cell lymphoma (DLBCL) who were treated with either up-front autologous stem cell transplantation (ASCT) or salvage chemotherapy followed by delayed ASCT after relapse. Data for 122 DLBCL patients who underwent ASCT as up-front or salvage treatment were analyzed. The 3-year overall survival (OS) rate in DLBCL patients who underwent up-front ASCT was 76.6%, and the rate for those who underwent delayed ASCT was 60.9% ($p = 0.017$). In a subgroup analysis of patients with a high-intermediate/high-risk age-adjusted International Prognostic Index, achievement of complete remission translated into improved OS in the up-front ASCT group, whereas patients who achieved partial remission had similar OS rates in both groups. The up-front ASCT group had improved OS in patients aged <50 years or with good performance status, whereas the OS rates of both groups were similar in patients aged ≥60 years or with poor performance status. When the OS outcome is analyzed by the number of factors (no complete remission during R-CHOP induction chemotherapy, age ≥50 years, and performance status ≥2), the 3-year OS rates of patients with zero or one, two, and three clinical factors were 80.2%, 51.6%, and 0%, respectively ($p < 0.001$). In conclusion, in higher-risk DLBCL patients, induction chemotherapy followed by up-front ASCT may have a survival benefit compared with induction chemotherapy alone in highly selected patients who have achieved a complete remission, who are aged <50 years, and who have a good performance status at diagnosis.

First-line chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens in combination with rituximab (R-CHOP) are the current standard treatments for CD20+ diffuse large B-cell lymphoma (DLBCL); the 3-year overall survival (OS) rate with these regimens is 75.3% [1]. However, both the 5-year progression-free survival (PFS) and OS rates are still <60% in patients with high or high-intermediate risk according to the International Prognostic Index (IPI) [1,2]. Gisselbrecht et al. reported that only 21% of patients with relapsed aggressive lymphoma previously treated with rituximab achieved a durable remission after salvage treatment [3], indicating that

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0301-472X/
http://dx.doi.org/10.1016/j.exphem.2015.08.008

improvement in first-line treatment in high-risk patients is a key issue.

High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) is a well-established and important treatment for aggressive lymphoma; it is considered the best treatment for DLBCL patients with relapsed disease who still respond to salvage therapy [4]. However, DLBCL is frequently resistant to chemotherapy, resulting in recurrence with unsatisfactory outcomes [3,5]. Such patients may be cured by aggressive up-front treatment with HDT/ASCT. In the pre-rituximab era, several trials documented prolonged PFS or event-free survival (EFS), but not OS, with HDT/ASCT as first-line therapy in patients with aggressive lymphoma [3,6–8]. Two meta-analyses of up to 11 randomized trials reported a similar OS in patients regardless of whether they were treated with up-front ASCT or standard induction chemotherapy [9,10].

Meanwhile, in the rituximab era, the results of several randomized trials of up-front ASCT in high-risk patients were recently reported. In the randomized phase II trial of the DSHNHL, which compared dose-dense R-CHOEP14 to dose-escalated R-CHOEP plus HDT/ASCT, there were no differences in PFS and OS between groups [11]. The SWOG S9704 trial compared CHOP ± R chemotherapy and CHOP ± R followed by up-front ASCT in younger high-risk (age-adjusted [AA]-IPI = 2–3) DLBCL patients. ASCT improved PFS in patients who had a response to induction therapy, but this did not translate into a survival advantage [12]. However, in this study, 54% of patients did not receive rituximab and several patients with other than DLBCL were enrolled. Therefore, we await the results of currently ongoing randomized trials by major cooperative groups to address the role of up-front HDT/ASCT for high-risk DLBCL patients in the rituximab era. Furthermore, no study has been conducted to compare the outcome of up-front ASCT after immuno-chemotherapy with that of salvage chemotherapy followed by delayed ASCT after relapse in high-risk DLBCL patients who attain a response during induction chemotherapy. It is also possible that there are clinical factors that can be used to identify high-risk DLBCL patients who may benefit the most from up-front ASCT.

The aims of our retrospective study were to compare the outcome of R-CHOP induction chemotherapy followed by up-front ASCT with that of salvage chemotherapy followed by delayed ASCT after relapse in DLBCL patients, and to identify clinical factors that define the high-risk DLBCL patients who have improved outcome from up-front ASCT.

Methods

Patients

Twelve centers of the Consortium for Improving Survival of Lymphoma (CISL) participated in this study. The clinical outcomes of DLBCL patients diagnosed between May 2005 and February 2013 who underwent HDT followed by ASCT were assessed. All centers completed an extensive case report form for every eligible patient. Follow-up questionnaires were used to obtain missing data.

Overall, the clinical data of 191 patients diagnosed with DLBCL were collected. Among them, 57 patients were excluded because of induction treatment with CHOP chemotherapy without rituximab, 2 because of concomitant central nervous system involvement, and 10 because of refractory disease after induction chemotherapy (Fig. 1). Finally, the data for 122 DLBCL patients who achieved complete remission (CR)/partial remission (PR) during induction chemotherapy and underwent ASCT as up-front or salvage treatment were analyzed. All patients received R-CHOP chemotherapy as first-line treatment.

This study was approved by the institutional review board of each institution. All patients provide written informed consent before R-CHOP induction chemotherapy.

Response and follow-up

Tumor responses were classified according to the revised response criteria for malignant lymphoma [13]. A CR was defined as complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy. Unconfirmed CRs were assigned to the CR category. A PR was defined as at least a 50% decrease in the sum of the products of the diameters of up to six of the largest dominant nodes or nodal masses. Refractory disease was defined as no response or progressive disease after chemotherapy. Response to HDT/ASCT was assessed 2 or 3 months after ASCT. Patients were re-evaluated every 3 months for the first 2 years after ASCT, every 6 months for the following 3 years, and then yearly or when clinically required.

Statistical analysis

Between-group comparisons were conducted using a two-sided independent t-test or a Wilcoxon rank-sum test for continuous variables, and a χ^2 test or Fisher's exact test for categorical variables.

Overall survival was analyzed with respect to timing of ASCT (i.e., up-front ASCT vs. delayed ASCT) after achievement of a response to R-CHOP chemotherapy. OS was measured from the achievement of response after R-CHOP induction chemotherapy to the date of death or final follow-up. The difference between the Kaplan–Meier curves for OS was assessed using the log-rank test. The level of significance was set at $p < 0.05$. All statistical analyses were performed using SAS 9.3 for Windows.

Results

Patient characteristics

The characteristics of the 122 patients are summarized in Table 1. The median age was 50 years (range: 15–65 years), and the median time from response to R-CHOP chemotherapy to transplantation was 10 months (range: 4–90 months). Ninety-four patients (77.1%) presented with advanced stages (III/IV). Moreover, 35 (28.7%) and 21 patients (17.2%) had B symptoms and bulky mass, respectively. At the time of diagnosis, 62 (50.8%) patients were classified as being at high-intermediate/high risk according to the IPI scoring system, and 72 (59.0%) patients were classified as being at