Pretreatment prognostic factors and outcome in patients with relapsed or primary-refractory diffuse large B-cell lymphoma treated with second-line chemotherapy and autologous stem cell transplantation

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The age-adjusted International Prognostic Index assessed before salvage therapy with ICE (ifosfamide, carboplatin, etoposide) predicts outcome in patients with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL). Patients can be stratified according to this index into favorable and unfavorable cohorts. Subsequently we attempted to determine if the cell of origin as determined by immunohistochemistry would predict outcome, as it had in the first-line setting. However, none of the molecular markers, which are prognostic in first-line therapy, nor immunohistochemical classification by cell of origin, relate to survival outcome of DLBCL patients in the second-line setting, implying that dose intensification of therapy can overcome the prognostic import of these unfavourable risk factors.

Key words: diffuse large B-cell lymphoma (DLBCL), ICE (ifosfamide, carboplatin, etoposide) regimen, rituximab, autologous stem cell transplantation, prognostic factors, DNA microarray

introduction

While CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, with or without the addition of rituximab, is capable of inducing a complete response (CR) leading to cure in a proportion of patients with diffuse large B-cell lymphoma (DLBCL), nearly 50% of patients have primary refractory disease or experience a relapse.

At the Memorial-Sloan Kettering Cancer Center, the standard approach to relapsed or primary refractory DLBCL is to treat clinically eligible patients with second-line chemotherapy based on the ICE (ifosfamide, carboplatin, etoposide) regimen. Peripheral blood progenitor cells (PBPCs) are collected following the third cycle. Patients who achieve a CR or partial response (PR), i.e. those with chemosensitive disease, subsequently receive myeloablative high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). Prior to HDT, patients with two or fewer involved fields receive accelerated fractionation radiation therapy up to a dose of 36 Gy.

Since HDT/ASCT is confined to patients with CR or PR, factors other than chemosensitivity must be influencing survival since less than 35% of transplant-eligible patients are cured with this approach. It would be helpful to ascertain these factors so that intensity of second-line treatment can be adapted to the individual patient’s degree of risk.

overall experience with HDT/ASCT

Intent-to-treat analysis of data from 147 patients with relapsed or refractory DLBCL shows that a third survive beyond 4 years, at which point the cumulative survival curve reaches a plateau extending to 10 years. Of the 99 patients in this series who had HDT/ASCT, 45% lived beyond 4 years. Attaining a CR with ICE appears to confer benefit [1]. Among the 38 such patients, 55% were alive at 4 years. This compares with 40% long-term survival among patients with a PR prior to transplant ($P = 0.16$).

This raises the question of whether adding rituximab to the ICE regimen (R-ICE) in CD20+ DLBCL can increase the proportion of patients in remission at the time of transplant, and hence the chances of an improvement in event-free survival. Rituximab is given at 375 mg/m$^2$ on day 1 of each cycle (and on days 1 and 2 of the first cycle), with ifosfamide 5 g/m$^2$ mixed with an equal dose of mesna given over 24 h starting on day 4. Also on day 4, patients receive carboplatin to an AUC of 5 (with maximum dose 800 mg). Etoposide 100 mg/m$^2$ is administered on days 3, 4 and 5. Prophylactic G-CSF is given on days 7–14 at 5 µg/kg during cycles one and two, 10 µg/kg in cycle three and continuing through leukapheresis.

In the 36 patients who have been treated with R-ICE (70% of whom had relapsed disease), the PET-confirmed CR rate is 56% [2]. This compares with a 26% CR rate among 163 historical controls from the pre-rituximab era who were treated with ICE alone ($P = 0.001$). Although numbers to date are small and the historical controls somewhat different in clinical
features (e.g. only 35% had relapsed disease), this increase in CR rate is substantial. It is not yet possible to say that it translates into improved event-free survival. However, the 4-year event-free survival among 36 patients treated with R-ICE approaches 60% (Figure 1).

It may be important to note that these 36 patients were rituximab-naïve. It is not known whether the effect of second-line rituximab will be as marked among patients who have already been treated with R-CHOP. Despite 8 days of prophylactic G-CSF, the addition of rituximab to ICE increased neutropenia. As a result, a move has been made to the 21-day regimen now used in the CORAL study (see Hagberg et al. [3]).

Also relevant here is experience at the University of Nebraska Medical Center [4]. Vose and Sneller report 60% 1-year EFS and 72% overall survival among 28 relapsed/refractory B cell NHL patients treated with an outpatient regimen of R-ICE. Among the 19 stem cell transplanted patients, EFS was 70% and OS 82%.

clinical prognostic factors

Long-term follow-up of Memorial-Sloan Kettering Cancer Center patients treated with ICE-based salvage regimens and ASCT has revealed several important insights into factors affecting survival. First, in patients who respond to second-line ICE, overall survival among those whose disease had been refractory to first-line CHOP is not significantly worse \( (P = 0.2) \) than that in patients who responded to first-line and then relapsed [5]. In this respect, the 99 patients in the chemosensitive subgroup differ from the wider second-line population. In the overall series of 147 patients, those who relapsed after response to CHOP did have a greater chance of survival than those whose disease was refractory to first-line therapy \( (P = 0.016) \).

Secondly, overall survival can reliably be predicted using three simple risk factors—stage III/IV disease, serum LDH level greater than normal and Karnofsky performance status less than 80%—evaluated at the start of therapy with ICE [6]. Patients with none of the three age-adjusted International Prognostic Index (aa-IPI) risk factors have a greater than 70% chance of surviving to 5 years, while those with all three risk factors have a less than 20% chance. Patients with intermediate risk have intermediate survival and the overall relationship between IPI and outcome is highly significant \( (P < 0.00001) \) (Figure 2).

outcome according to molecular markers

The implication of the above is that second-line treatment for primary refractory and relapsed DLBCL should be adapted according to clinical risk factors, as is the case with initial treatment. However, outcome varies widely even among patients with the same clinical features. It is therefore clear that assessment of risk needs to become far more sophisticated. One element is a more refined molecular classification of the disease.

DNA microarray analysis reveals patterns of gene expression that predict survival following chemotherapy [6]. DLBCL appears divisible into at least three distinct diseases: germinal centre B-cell-like (GCB), activated B-cell-derived and type 3. According to the gene array work of Rosenwald et al. [6], the probability of survival at 8–10 years is approximately 50% for patients with GCB disease, but closer to 30% for patients with activated B-cell-like or type 3 tumors.

A similar conclusion is justified by Hans et al.’s immunohistochemical classification of DLBCL by staining for CD10, bcl6 and MUM1 [7]. On this system, patients with a DLBCL classified as GCB had a 76% chance of 5-year survival.
following CHOP chemotherapy. For patients with non-GCB DLBCL, the 5-year survival rate was only 34%.

However, molecular markers, which are prognostic in the first-line setting, may not be predictive in second-line patients. In the Memorial-Sloan Kettering Cancer Center series described above, tissue specimens obtained from 88 patients before ICE therapy were analyzed by microarray [8]. Positivity was defined by the percentage of cells marked by a range of antibodies. Cell of origin was also determined by IHC. Germin al centre-derived tumors were defined as CD10+ or bcl6+ and MUM1-. Non-germin al centre tumors were defined as being CD10- and MUM1+, or CD10- and bcl6-.

In this study of the outcome of second-line therapy, markers such as MIB1, MUC1-mucin, MDR, p53 and bcl2 were not predictive of survival at 5 years (Table 1).

Furthermore, Hans’ classification of tumors by cell of origin into GCB- and non-GCB-derived (which had proved so predictive in patients with untreated disease) had no bearing on outcome in these relapsed or primary refractory patients.

Four-year survival was close to 40% both in the 54 patients with non-GCB disease and in the 34 with GCB-derived tumors.

Cell of origin was unrelated to second-line outcome both for the relapsed/refractory population overall and in the 67 patients whose relapsed or refractory disease subsequently proved chemo sensitive (Figure 3).

Clearly, new molecular markers relevant to outcome in the second-line setting must be sought and further microarray studies are ongoing.

### references


### Table 1.

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### Figure 3.