Therapy of diffuse large B-cell lymphomas

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The results of the Intergroup Study published by Fisher and colleagues, which demonstrated that the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen was as effective and less toxic than the more intensive regimens of the so-called 2nd and 3rd generations, indicated that more important than the choice of a chemotherapy regimen is the selection of patients eligible for a trial [1]. As a consequence, the International Prognostic Index (IPI) was established, which enables the assignment of patients to one of four (low, low-intermediate, high-intermediate and high) risk groups with a significantly different outcome [2]. Young good-prognosis patients comprise the low and low-intermediate risk groups (risk factor 0 and 1 according to the age-adjusted IPI [2]) while poor-prognosis patients comprise the high-intermediate and high risk groups ($\geqslant$ two risk factors). Optimal treatment results in young good-prognosis patients have been achieved in the MInT study with six cycles of a CHOP-like chemotherapy in combination with the anti-CD20 antibody rituximab. Using this therapeutic approach, 3-year event-free survival rates of >90% and overall survival of >97% can be achieved in a *very favourable subgroup* (patients without IPI risk factor and no bulky disease), while further improvement is warranted for the *less favourable subgroup* (IPI = 1 and/or bulky disease; 3-year event-free survival: 77%) [3]. A subgroup analysis of the MInT study confirmed the superiority of CHOP plus etoposide (CHOEP) compared to CHOP alone. However, after the addition of rituximab, the advantage of CHOEP over CHOP disappeared making the less toxic CHOP the ideal chemotherapy partner for rituximab in the treatment of diffuse large B-cell lymphoma (DLBCL) and indicating that differences between different chemotherapy regimens fade or completely disappear when combined with rituximab, which appears to function as a "chemotherapy equaliser". The nearly 100% overall survival of young patients with a very favourable prognosis suggests that at least some of these patients are overtreated and reduction of therapy should be possible without putting the excellent prognosis of these patients at risk. Therefore, in the FLYER study being carried out by the DSHNHL, young patients of the very favourable risk group are randomised into either four or six cycles of CHOP-21, both in combination with six applications of rituximab. Other approaches use a combination consisting of three cycles of R-CHOP-21 followed by involved-field radiation [4]. For the young less favourable subgroup (bulky disease and/or one risk factor according to the aaIPI), trials are ongoing that include a German trial comparing the MInT standard of six cycles of R-CHOP-21 with dose-dense R-CHOP-14 (the DSHNHL's UNFOLDER study) and a French GELA study comparing both dose-dense and dose-escalated ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone).

For young poor-prognosis patients, 5-year survival is approximately 60%, and progress has not been convincingly or specifically demonstrated in this patient group. While several randomised trials comparing conventional doses with primary high-dose chemotherapy and stem-cell transplantation have not convincingly shown an advantage for this aggressive treatment approach in the pre-rituximab era, ongoing studies are evaluating the role of this strategy in combination with rituximab. In the Mega-CHOEP study of the DSHNHL, a dose-escalated CHOEP followed by three cycles of Mega-CHOEP [5], each necessitating stem cell support, are compared with eight cylces of dose-dense R-CHOEP-14. In a similar approach, an Italian study is comparing dose-dense R-CHOP-14 with early high-dose chemotherapy and stem cell support. These studies will show whether dose-dense conventional or high-dose chemotherapy regimens requiring stem cell support in combination with rituximab will result in improvements for young poor-prognosis patients.

In elderly patients with DLBCL, both interval reduction from 3 (CHOP-21) to 2 weeks (CHOP-14) and the addition of rituximab to eight cycles of CHOP-21 improved the outcome of these patients to a similar degree without increasing toxicity [6–8]. Thus, eight

cycles of R-CHOP-21 or six cycles of CHOP-14 became the standard regimens for elderly patients with DLBCL. The RICOVER-60 trial assessed whether combining dose-dense CHOP-14 with rituximab could further improve outcomes of elderly patients with DLBCL. These patients (aged 61–80 years, stages I–IV) were randomised to receive six or eight cycles of CHOP-14 each with or without eight applications of rituximab. Of 1222 patients, six cycles of CHOP-14 with eight applications of rituximab yielded the best results with respect to response rates, event-free, progression-free and overall survival. Compared to the previous German standard of 6×CHOP-14, only six, not eight, cycles of CHOP-14 in combination with eight applications of rituximab significantly improved overall survival compared to 6×CHOP-14 [3]. The results obtained with six cycles of CHOP-14 in combination with eight applications of rituximab are the best reported today both for good-prognosis and poor-prognosis elderly patients with DLBCL. Whether dose densification can improve the results in elderly patients treated with R-CHOP (R-CHOP-21 versus R-CHOP-14) is being addressed by a complimentary study of the GELA which has recently completed recruitment. Until the results of this French trial become available and since a further intensification of chemotherapy in the elderly population beyond R-CHOP-14 does not appear to be promising, because of the risk of being counterproductive (due to dose reductions and treatment delays which are often necessary in this population), novel approaches are evaluating the role of dose-dense rituximab in combination with six cycles of CHOP-14. Early results of the DENSE-R-CHOP-14 in elderly patients with DLBCL suggest that dose-dense rituximab can improve the outcome of elderly poor-prognosis patients with DLBCL [9]. In summary, unprecedented improvements of outcome of patients with DLBCL have been achieved during the last ten years, but further efforts in the form of large prospective and – whenever possible – randomised trials are necessary in order to solve the remaining problems in the treatment of aggressive lymphomas.

Conflict of interest statement

Author is a member of the Roche MabThera Advisory Board.

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