Is CHOP the standard of therapy for poor-prognosis large-cell lymphoma?

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The best therapy for advanced large-cell lymphoma is unknown since among the current chemotherapeutic programs no single regimen has emerged with therapeutic superiority and tolerable toxicity. In a study by Fisher, data were derived from the prospectively randomized trial of the Southwest Oncology Group (SWOG) which compared CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) to m-BACOD, ProMAC- Cytosar, and MACOP-B [1]. The case for more aggressive cytotoxic therapy has been made by Gianni et al. using data from a trial comparing MACOP-B to an extended program of chemotherapy administration followed by high-dose therapy and autotransplantation [2]. In both series, patients with classic large-cell lymphoma were included, but not all patients were in the high-risk prognostic group based on the widely accepted International Prognostic Index. In fairness, Dr. Fisher does not advocate CHOP as the treatment of choice per se but rather emphasizes the need for clinical trials of new and, if necessary, more intensive treatment for large-cell lymphoma since more than 60% of the patients in the SWOG trial have relapsed on long-term follow-up. Clearly, regimens developed in single institutions with a high order of selectivity, especially leaning to younger patients with favorable prognostic features, do not offer more than CHOP, which, if nothing else, is relatively straightforward in design and schedule. Of course, the potential negative spin-off of this trial is that patients with large-cell lymphoma are not referred for innovative treatment programs because CHOP can be easily given in a community setting. The SWOG trial emphasized how poor the outcome of CHOP and other regimens can be with adequate follow-up, with less than 50% cured. The International Prognostic Index study emphasized that poor prognostic patients had a 20%–30% five-year disease-free survival [3]. The benefits of CHOP and/or other similar modified regimens are directly proportional to clinical prognostic factors outlined in the International Prognostic Index. For poor-prognosis patients, clearly, new treatments are needed.

In a study by Gianni, data were derived from a prospectively randomized comparison of MACOP-B to his high-dose alternative following sequential use of active agents prior to ABMT (unpublished data). The data are interesting and, although based on relatively small numbers, show a superiority for the more intensive arm. While this is not a definitive study, it does suggest that dose intensification might offer a measurable advantage to some patients in the poor-prognosis groups. This is further suggested by the GELA Group study which compared early intensification with autologous transplantation (ABMT) and high-dose therapy with combination chemotherapy alone in patients who have achieved an initial complete remission [4]. A follow-up of that data has shown an emerging significant advantage to patients in the high-risk group (International Prognostic Index) who received early intensification. The large numbers of patients in the other prognostic groups in the trial did not derive a survival benefit from early ABMT once a complete remission was achieved. This suggests that in the more favorable groups, failure and subsequent death are less than in higher risk groups but, in the latter, are more likely due to drug resistance which cannot be overcome by ABMT. In contrast, patients in the high-risk prognostic group showed a lower complete remission rate and a high failure rate in general. A fraction of these results may be corrected by dose intensification over and above that achieved by CHOP or similar regimens. It is also clear that sensitivity to chemotherapeutic agents is the sine qua non for durable remissions following ABMT—thus, the GELA data suggest that consolidation with ABMT in poor-risk patients who achieve a CR is superior to conventional-dose chemotherapy. The data, although statistically significant (P = 0.01) show only a small margin of benefit of 10%–18%. The margin of benefit in patients who would have achieved only a partial remission is uncertain, but some data from the Netherlands in a varied group of patients suggest minimal or no added survival benefit to performing ABMT [5]. Further, the GELA Group attempted to improve the lower CR rate of poor-risk patients by early intensification with BEAM (BCNU, etoposide, ara-C, melphalan) autologous stem-cell transplantation following three cycles of chemotherapy (LNH 93-3). This was compared with standard-dose combination chemotherapy. The data in 302 randomized patients show no increase in CR rate or freedom from relapse was achieved. In fact, event-free survival and overall survival were better in the chemotherapy only group [6]. Dose intensification without ABMT in poor-prognosis patients has been tested in a pilot series of 30
patients with a regimen of four cycles of augmented CHOP (mega-CHOP) with cyclophosphamide at 3 g/m². The encouraging results of this regimen (90% CR and 69% event-free) must be balanced against the toxicity. An interesting tangential observation was high correlation of reversion to a negative gallium-67 scan after two courses and favorable outcome [7]. The minimum quantity of intensive chemotherapy to achieve long-term cure is unknown and is likely to vary by tumor bulk and intrinsic drug sensitivity. This is supported by the fact that cures can be achieved, albeit fewer in number in patients who present with poor progonostic features.

In summary, Fisher’s data from the SWOG trial suggest that basically minor modifications of the CHOP regimen, such as m-BACOD, complex regimens with multiple agents (Pro-MACE/Cytobom), or a 12-week package of combination chemotherapy with frequent (weekly) treatments of MACOP-B offer no measurable advantage. The Gianni data suggest that an innovative program of sequential intensive chemotherapy culminating in ABMT offers a significant survival advantage over MACOP-B in poor-risk patients with large-cell lymphoma. Accepting the element of selection and the relatively low numbers, these data suggest that the dose intensification option should be further investigated, especially in poor-risk patients. The true margin of benefit is statistically unknown at present, but, based on the GELA data, it might be quite small. Dr. Fisher is in agreement with the pursuit of such innovations in lymphoma therapy but cautions that prospective controlled trials will be needed to extract the real answer as to the increment of benefit that is to be derived from dose intensification in the initial treatment.

References


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