Improving on the efficacy of CHOP

The standard regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) given over a 3-weekly cycle (CHOP-21) was easy to use and produced acceptable response rates. However, it did not provide a long-term survival benefit for most patients – only about 40% of patients had long-term disease control.3 Several attempts were therefore made to improve on the efficacy of this regimen, using conventional chemotherapy.

Treatment with doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVP)-14, in which the doses of both doxorubicin and cyclophosphamide are higher than in the standard CHOP regimen, was originally devised as a standard treatment for all T-cell lymphomas. In two studies, there was a significant improvement in favor of ACVP, compared with CHOP-21, in patients who were older and had a poor prognosis,4 and in those who were young and had a good prognosis,5 although ACVP was more toxic than CHOP. In a third study, ACVP was shown to be more effective than methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) in patients with low-risk aggressive lymphoma.6

Increasing the dose intensity of CHOP by reducing the dose interval from 3 to 2 weeks (CHOP-14) produced a clear increase in efficacy in both young and elderly patients.7 Another study investigated the efficacy of ACVP regimens followed by either sequential high-dose chemotherapy or intensive chemotherapy plus autologous bone marrow transplant, in patients with a high International Prognostic Index (IPI). Bone marrow transplant was associated with 64% overall survival in the long term.8 Thus, this was the level of response and efficacy that could be produced in patients with a poor prognosis, prior to the introduction of rituximab therapy.

Improving on the efficacy of R-CHOP

The efficacies of R-ACVB P and R-CHOP were compared in the LN H03-2B study (clinicaltrials.gov identifier NCT00140595), which involved young patients with DLBCL and an age-adjusted IPI of 1. An interim analysis showed superiority of R-ACVP-14 over R-CHOP-21 in terms of 2-year event-free survival. The final analysis, recently presented at the 11th International Conference on Malignant Lymphoma, confirmed these results.17

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Key words: non-Hodgkin's lymphoma, treatment, chemotherapy, rituximab.

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Improving on the efficacy of R-CHOP

The efficacies of R-ACVB P and R-CHOP were compared in the LN H03-2B study (clinicaltrials.gov identifier NCT00140595), which involved young patients with DLBCL and an age-adjusted IPI of 1. An interim analysis showed superiority of R-ACVP-14 over R-CHOP-21 in terms of 2-year event-free survival. The final analysis, recently presented at the 32nd American Society of Hematology Annual Meeting in December 2010, confirmed a significant advantage for R-ACVP at 3 years in terms of event-free, progression-free, disease-free, and overall survival.18

There is little evidence for how best to treat patients with 2-3 adverse prognostic factors, although historically outcomes have been poor. A retrospective analysis of patients with DLBCL treated with R-CHOP showed that response rates were good for patients with 0-2 adverse prognostic factors, but 4-year progression-free survival and overall survival rates were only just over 50% for patients with more than two adverse

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Adapting treatment to individual patient risk
An initial study of the use of [18 F]fluoro-2-deoxy-D-glucose positron emission tomography (PET) before treatment, after two cycles, and after four cycles showed that it was possible to identify those patients who were PET-negative early in treatment, and thereby to predict with a high degree of accuracy those who would remain disease-free (Figure 2). Further studies have refined these assessment methods, to reduce the incidence of false-positives and help develop standardized techniques and criteria that can be widely used. Based on these initial results, a Phase II study (LNH2007-3B) has been started to follow PET changes under two treatment regimens, namely R-CHOP-14 and R-ACVB P-14, in patients with DLBCL and an age-adjusted IPI of 2-3. PET scans will be performed at baseline, and after two and four cycles, and treatment adapted after cycle 4 depending on the PET results.

Treatment of follicular lymphoma
Follicular lymphoma usually grows and spreads slowly, and has few symptoms. The current goal of therapy is to maintain the best quality of life for patients and to treat them only when they develop symptoms. Any therapeutic approach should demonstrate an improvement in patient survival but, because median survival is 14-15 years, surrogate markers such as progression-free survival are needed to assess possible survival benefits.

Randomized trials clearly demonstrated that the addition of rituximab to the commonly used chemotherapies increased patient response rates and survival. Therefore, these patients should receive rituximab in addition to chemotherapy. Two studies have also investigated the effects of maintenance therapy in patients who responded to initial treatment. One reported the use of yttrium-90-ibritumomab tiuxetan versus no further treatment for patients who showed a complete or partial remission, and showed an advantage for maintenance treatment over the watch-and-wait strategy. A second study (PRIMA), completed in 2007, included 1193 patients, 74% of whom had received previous R-CHOP and 23% of whom had received previous rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). The results were in favor of rituximab maintenance therapy, compared with observation alone. After a median follow-up of 36 months, progression-free survival was 74.9% among those receiving rituximab versus 57.6% in the observation group (P<0.0001).

Conclusions
CHOP has long been the standard therapy for lymphoma. Improvements have been made to the efficacy of this regimen by increasing the dosing frequency, increasing the doses (in the ACVB P regimen), and by adding rituximab immunotherapy to either of these regimens. Research is now underway to investigate the place of new therapies such as lenalidomide, new immunotherapies, and high-dose rituximab in improving patients’ overall survival (see Burchardt in this supplement).
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