Salvage Therapy for Diffuse Large-Cell Lymphoma

Since its recognition as a clinical-pathologic entity in the late 1960s, diffuse large cell lymphoma (DLCL) has challenged the imagination and the ingenuity of cancer chemotherapists. DLCL is the most common form of aggressive non-Hodgkin's lymphoma, a group of diseases that leads to a rapidly fatal outcome if unsuccessfully treated. Radiotherapists quickly learned that, unlike Hodgkin's disease, a single node or a single extranodal site could be cured by local radiotherapy reinforced with chemotherapy, but all other stages required systemic treatment. The early experience with combination-chemotherapy regimens modeled after MOPP produced long-term disease-free survival in 30% to 40% of patients; subsequent efforts to improve conventional chemotherapy have produced further progress, with 3-year disease-free survival of perhaps 60% for a number of different regimens.

This journal carries a report from Stanford of a new regimen of moderate toxicity designed to treat patients with aggressive lymphoma who have failed prior therapy or who could not be safely treated with a doxorubicin-containing regimen. The primary innovation is the use of etoposide in a C-MOPP-like regimen with cyclophosphamide, procarbazine, and prednisone with or without bleomycin. The results in 22 patients with DLCL who had failed first-line therapy were impressive: 8 (36%) achieved a complete response and 9 (41%) a partial response. When other histologies of aggressive lymphoma are included, the complete-response rate in 61 patients remained 34%. The complete responses are the most significant results, in that partial responses rarely produce substantial clinical benefit in this aggressive disease. These CEPP(B) results compare favorably with other salvage regimens, such as the MIME (methyl-GAG, ifosfamide, methotrexate, etoposide [VP-16]), which gave a 32% complete-response rate in patients with aggressive histology, and DHAP (dexamethasone, high-dose cytosine arabinoside, and cisplatin), which produced a 29% complete-response rate in patients with relapsed or refractory DLCL.

One cannot make solid comparisons among MIME, DHAP, and CEPP(B) because patient characteristics may not have been the same. For example, the CEPP(B) patient series included a preponderance (42 of 61) of patients who had experienced a complete response to initial therapy, while in the MIME and DHAP studies the majority of patients had not achieved a complete response with their primary treatment. The DHAP experience was noteworthy for the 27% complete-response rate in the subgroup of patients refractory to initial induction chemotherapy. In addition, 53 of 61 in the CEPP(B) series had an excellent performance status, and the vast majority had small tumor bulk, a normal LDH, and no systemic symptoms at the time of salvage treatment. Thus, the CEPP(B) experience was obtained in a favorable group of relapsed patients. Furthermore, it is unclear from the Stanford report whether any patients had actually failed attempts at re-induction with the primary treatment regimen or, in other words, were clearly drug resistant. The exclusion of true re-induction failures might explain the impressive results from a regimen that contained at least two drugs (cyclophosphamide and prednisone) likely included in the patients' initial treatment experience.

What is the importance of this report? While 9 of 14 previously untreated DLCL patients achieved complete response, the investigators admit that they would not advocate the use of CEPP(B) as initial treatment except in those patients unable or unwilling to take an anthracycline-containing regimen. Clinicians should be cautious in relinquishing doxorubicin for DLCL. A recent report from Stanford indicates that, in an analysis of three regimens for DLCL, the dose intensity of doxorubicin was the single strongest predictor of treatment outcomes; indeed, one might argue that total doxorubicin doses of 250 mg/m², as administered in most intensive DLCL regimens, represent a minimal danger to patients with coronary artery disease in the absence of overt congestive heart failure. This point needs to be studied in a careful prospective manner, and until that is done, CEPP(B) represents a reasonable alternative for those unwilling to take the chance with doxorubicin.

A more pertinent question is the possible role of CEPP(B) for salvage therapy. In relapsed DLCL patients with favorable prognostic features the regimen could serve as a prelude to autologous bone marrow transplantation (ABMT). In this favorable group, at least 34% would qualify for ABMT by virtue of attaining a complete remission, and an additional untold number could also be thus treated if they achieved a 90% or greater response. The regimen has the distinct advantage of minimal toxicity, probably less than the toxicity of DHAP or MIME, which produced fatal side effects in 8% and 6% of patients, respectively, as compared with 1% for CEPP(B). Here again, though, the results should be interpreted cautiously, as the patient populations were not obviously equivalent. While the modest toxicity of CEPP(B) is encouraging, its value in refractory (drug-resistant) patients needs to be established.
As mentioned previously, the regimen contains a "new" agent, etoposide, that shares cross-resistance in multidrug-resistant (mdr) cells and in topoisomerase-II mutant cells with doxorubicin. However, it is true that cross-resistance between the two agents is often incomplete. The investigators are not convinced that bleomycin plays a useful role in the regimen and recommend its deletion, and procarbazine is not often used in DLCL because of its limited single-agent activity. A strong argument could be made for salvage regimens based on other rationales, such as the use of other non–cross-resistant drugs (cisplatin or carboplatinum, ifosfamide rather than cyclophosphamide); greater dose intensity of the alkylating agent; colony-stimulating factors to rescue bone marrow function and allow dose escalation; or prolonged infusion or mdr-type drugs, because this schedule is more effective against mdr-type cells. Among these possibilities, drug resistance has particular relevance as the basis for salvage strategies, in that the clinical setting of salvage therapy represents the outgrowth of resistant tumor cells from an initially responsive population. Evidence is mounting that a fraction of relapsed DLCL patients, still incompletely quantified, will have tumors positive for the P-170 glycoprotein that mediates classical multidrug resistance.

Given the rapid progress being made in defining the biochemical lesions that underlie drug resistance in the lymphomas, it is quite likely that we will soon be able to test resistance-reversal strategies in such patient populations, and to some degree tailor the regimen to the tumor. Because of the ready access to tumor in superficial lymph nodes, DLCL offers unique opportunities for studying drug resistance in the clinic and has already become the subject for prototype resistance-reversal protocols using agents that block P-170 glycoprotein function. At the National Cancer Institute we are testing a multi-agent 4-day infusion regimen that includes etoposide, doxorubicin, vincristine, and cyclophosphamide; our plan is to add R-verapamil as an mdr-reversing agent once the maximum-tolerated dose for chemotherapy is established. Initial rapid responses to infusion regimens in patients unresponsive to the same drugs administered in conventional bolus doses lead us to believe that simple changes in schedule may be beneficial in drug-resistant patients. Ultimately, such regimens, if successful in salvage patients, should logically be moved up front as initial therapy to improve the initial cure rate and to avoid the necessity for ABMT in the 50% of patients who currently fail primary therapy.

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REFERENCES

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