The Treatment of Patients With Aggressive Non-Hodgkin’s Lymphoma

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The curability of the aggressive, large-cell lymphomas was first convincingly reported by Levitt et al in 1972.[1] Patients with “reticulum cell sarcoma” were treated with a regimen that came to be known as COMLA (cyclophosphamide, vincristine [Oncovin], methotrexate, leucovorin, cytarabine [Ara-C]). A more commonly quoted paper was published in 1975 by DeVita et al describing the cure of advanced “diffuse histiocytic lymphoma” with COPP (cyclophosphamide, vincristine [Oncovin], procarbazine, prednisone).[2] During the 1970s the CHOP regimen (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) was described by McKelvey et al[3]; it quickly became the most widely used treatment for the aggressive large-cell lymphomas. Patients treated with two cycles of CHOP beyond documentation of a complete remission were often cured.[4]

Historical Attempts to Improve Upon CHOP

Over the next decade many other regimens were developed for the treatment of the illness that was by then called diffuse large-cell lymphoma or immunoblastic lymphoma. Included in these regimens were MACOP-B (methotrexate, doxorubicin [Adriamycin], cyclophosphamide, vincristine [Oncovin], prednisone, bleomycin, leucovorin),[5] ProMACE-CytaBOM (prednisone, doxorubicin [Adriamycin], cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine [Oncovin], methotrexate, leucovorin),[6] and m-BACOD (methotrexate, bleomycin, doxorubicin [Adriamycin], cyclophosphamide, vincristine [Oncovin], dexamethasone, leucovorin).[7] Each of these new regimens appeared to have a superior treatment outcome than what had previously been observed with CHOP. In fact, some physicians felt that it was unethical to continue to treat patients with the CHOP regimen. A large clinical trial was carried out in the United States where the CHOP regimen was compared to MACOP-B, ProMACE-CytaBOM, and m-BACOD. All four regimens were found to have an equivalent outcome, with approximately 35% to 40% of patients with bulky stage II, stage III, or stage IV disease achieving longterm, disease-free survival.[8] To many clinicians caring for patients with lymphoma, the comparability of CHOP to the more complicated regimens came as a surprise and a disappointment. The explanation for this outcome probably lies in patient selection, with lower-risk patients included in the phase II trials of the newer regimens. The development of the International Prognostic Index (IPI)[9] has allowed a much better method to predict treatment outcome for patients with aggressive large-cell non-Hodgkin’s lymphoma. Using the IPI there is a considerable spectrum of expected treatment outcomes for patients with Ann Arbor stage II, III, and IV disease. The net effect of the Intergroup trial was to discourage clinicians regarding the possibility of finding more effective combinations of existing drugs, and the CHOP regimen, based on less toxicity, became the standard treatment approach. However, as the papers in this supplement to ONCOLOGY illustrate, there is a new generation of regimens being developed for the treatment of patients with these disorders, and it appears that there are now superior options to CHOP.

Improved Understanding of the Disease

At the same time new treatment approaches were being developed for the treatment of patients with aggressive large-cell non-Hodgkin’s lymphoma, our understanding of the disorder has improved dramatically. In the mid-1990s a group of hematopathologists proposed a new way to classify non-Hodgkin’s lymphomas, taking into account immunologic, genetic, and clinical characteristics in
addition to histologic appearance of the tumors.[10] This system was shown to be not only clinically relevant, but also more reproducible than previous systems[11]; with minimal changes it was adopted as the World Health Organization classification for non-Hodgkin's lymphomas.[12] Most of the patients that would previously have been diagnosed as having diffuse large-cell lymphoma or immunoblastic lymphoma fit into the categories of diffuse large B-cell lymphoma or one of the subtypes of peripheral T-cell lymphoma. This new system also recognized the existence of mantle cell lymphoma, marginal zone lymphomas, and anaplastic large T/null cell lymphoma. The latter was an especially important category when considering the treatment of aggressive large-cell lymphomas, as it is an exception to the poor prognosis usually seen with peripheral T-cell lymphomas—at least when the anaplastic T/null cell lymphoma was shown to over express the alk protein.[13-16] Previous clinical trials have lumped diffuse large B-cell lymphoma in with the aggressive T-cell lymphomas. Because the overwhelming majority of patients in these trials had diffuse large B-cell lymphoma, the regimens found to be most effective were those most active in treating diffuse large B-cell lymphoma. It is very likely that the poor treatment outcome seen today with the aggressive peripheral T-cell lymphomas is because the regimens used have been chosen for their activity in diffuse large B-cell lymphoma. There is no reason to believe that these regimens would be the most active for the treatment of aggressive peripheral T-cell lymphomas, and in fact, completely different drugs may be superior. Until studies are done focusing specifically on peripheral T-cell lymphoma, it is likely that this problem will persist. New Regimens vs Standard CHOP:

Worldwide Clinical Trials
The papers from France, Germany, and Canada in this supplement to ONCOLOGY all strongly suggest that new regimens now exist for the treatment of diffuse large B-cell lymphoma that are more effective than CHOP. Bertrand Coiffier and Flix Reyes (see page 7) summarize the important series of clinical trials carried out by the Groupe d'Etude des Lymphomes de l'Adulte. These investigators were the first to show that the addition of the monoclonal antibody rituximab (Rituxan) to the CHOP regimen improved disease-free survival.[17] Although this trial was done in elderly patients, a subsequent trial carried out in Europe in younger, good-risk patients also showed an advantage to CHOP plus rituximab over CHOP alone.[18] Coiffier and Reyes also develop a strong argument that the ACVBP regimen—made up of an intensive remission induction with five drugs (doxorubicin [Adriamycin], cyclophosphamide, vindesine, bleomycin, and prednisone), central nervous system prophylaxis, and an intensive consolidation phase—is more active than CHOP. This has been shown to be true in randomized trials in patients with disseminated disease[19] and in those with localized diffuse large B-cell lymphoma.[20] We now need to know the comparative merits of ACVBP plus rituximab and CHOP plus rituximab. Rudolf Schmits, Norbert Schmitz, and Michael Pfreundschuh (see page 16) describe the results of a series of clinical trials from Germany that seem to have identified two regimens that are superior to traditional CHOP. These include CHOP plus etopoïde, which was particularly efficacious in younger patients, and dose-intensive CHOP—that is, CHOP at 14-day intervals supported by granulocyte colony-stimulating factor (filgrastim [Neupogen])-for older patients.[21] These treatment approaches have become standard in Germany. Once again, both of these regimens need to be combined with rituximab and compared to CHOP plus rituximab. Finally, Laurie Sehn and Joseph Connors (see page 26) from British Columbia carried out a study that showed without doubt that CHOP plus rituximab improved survival for patients with diffuse large B-cell lymphoma.[22] By comparing all patients in British Columbia treated in the 18 months before the introduction of rituximab with those treated in the 18 months following the introduction of rituximab, they found a 20% survival advantage after the drug was widely available. This is convincing proof of the impact of this treatment approach in an unselected population of patients.

Current Understanding and Future Directions
We are once again in an exciting era of the treatment of patients with aggressive non-Hodgkin's lymphoma. We now recognize the distinction between the peripheral T-cell lymphomas and diffuse large B-cell lymphoma and the need to study the former specifically. We know that patients with diffuse large B-cell lymphoma and those with aggressive peripheral T-cell lymphoma do not all have the same disease; subdivisions of both are becoming apparent. Genetic studies have identified at least two "diseases" that we currently call diffuse large B-cell lymphoma[20] and subdivisions of peripheral T-cell lymphomas are also evident.[12] Future studies are likely to identify subgroups of patients in which one regimen or another is likely to be especially efficacious. In this regard, there is increasing evidence that patients whose diffuse large B-cell lymphoma overexpresses the bcl-2 protein are those most likely to benefit from treatment with rituximab[23,24] Once again, the future for clinical research in the treatment of patients with aggressive non-Hodgkin's lymphoma looks bright.
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