

Treatment of Intermediate and High Grade Non-Hodgkin's Malignant Lymphomas

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The term non-Hodgkin's lymphomas (NHL) comprises a group of primary neoplasms of the lymphoreticular tissue involving stem cells and B or T lymphocytes in various degrees of differentiation.

We are going to discuss in this paper the various combinations used for the treatment of the intermediate and high grade malignancy NHL. Although there is some overlap among the classifications in use, most investigators would include in the above 2 groups all the diffuse types and only 1 nodular type.

These 2 groups differ in biological behavior, in response to treatment and in outcome. So, in the intermediate group median survival is longer than in the high grade group³, the neoplastic cells have a less rapid doubling time and, usually, they do not involve the CNS. The response rate to treatment is similar in the 2 groups, but the final outcome is different. In non-responders or in patients with partial remissions survival is significantly longer in the intermediate group. However, after complete remission the relapse rate is higher in patients of the intermediate group⁵ resulting in significantly fewer cures. These differences should guide us in planning treatment strategies.

The first very effective combination used was COP. This combination induced a 20-40% complete remission rate in both groups, and median survival was 8 months. The results were similar with the use of c-MOPP, but with this combination 40% of the 27 patients with diffuse histiocytic lymphoma achieved long-term disease-free survival¹. In our experience with 82 evaluable patients, 40.8% (Table 1) achieved complete remissions, and 63.6% of them remain disease-free from 39 to 142 months. Among patients in complete remission those with histiocytic (Figure 1) type histology have a better prognosis when achieving complete remission than the other histologic types, and this holds true in other series, too⁵.

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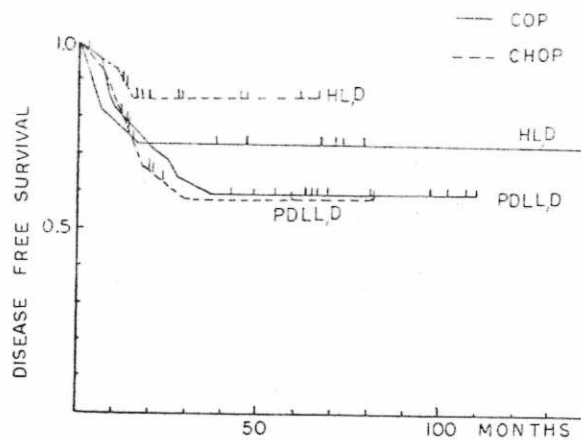


Figure 1 - Disease-free survival for patients with intermediate and high grade malignancy NHL after complete remission. Solid lines represent patients treated with COP and broken lines patients treated with CHOP. HL,D = histiocytic lymphoma, diffuse; PDLL,D = poorly differentiated lymphocytic lymphoma, diffuse.

Later, adriamycin was added to COP or other combinations. Its addition resulted in higher response rates and long-term survivals. The response rate increased to about 60%. Our experience is shown in Table 1, and again histiocytic lymphomas have a better prognosis (Figure 1) when achieving complete remission.

From 1976 and on, bleomycin, methotrexate with leucovorin rescue, nitrosureas, epipodophylotoxins and ara-C were included in many and various composite combinations. These combinations are more toxic, more difficult to manipulate, much more expensive and some need long hospitalization. However, they show increases in response rates and significant increase in median survival⁴. They are mainly used for the treatment of high grade malignancy NHL and it is too early to evaluate long-term disease-free survival. Our experience with B-CHOP, CHOP-methotrexate and ProMACE is limited. The response rate, including partial remissions, is almost 100%. Complete remission rate is 60-65%, but we have had several early relapses.

TABLE 1 - Response rates for high grade malignancy (HGM) and intermediate grade malignancy (IGM) non-Hodgkin's lymphomas, treated with COP and CHOP. CR = complete remission; PR = partial remission

	COP		CHOP	
	CR	PR	CR	PR
HGM	11 (40.8%)	8 (29.6%)	14 (58.4%)	5 (20.8%)
IGM	22 (40.7%)	18 (33.3%)	12 (63.2%)	4 (21.0%)
All	33 (40.8%)	26 (32.1%)	26 (60.5%)	9 (20.9%)

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⁵ STEWARD W.P., TODD I.D.H., HARRIS M., JONES J.M., BLACKLEDGE G., WAGSTAFF J., ANDERSON H., WILKINSON P.M., CROWTHER D.: *A multivariate analysis of factors affecting survival in patients with high-grade histology Non-Hodgkin's lymphoma.* Eur. J. Canc. Clin. Oncol., 20, 881-889, 1984.

The high grade malignancy NHL with the classic treatment timing (every 21 to 28 days) tend to relapse in between cycles or before bone marrow recovery. To overcome this problem new strategies have developed using in between cycles either non-myelotoxic agents (bleomycin and vincristine) or agents with minimal toxicity (methotrexate plus leucovorin rescue). More recently alternating non cross-resistant combinations are tried. These new strategies resulted in higher cure rates for high grade lymphomas².

The place of radiotherapy in the treatment of intermediate and high grade malignancy NHL is restricted by certain limitations. Therefore:

- 1) it is treatment of choice for stage IA and IA_E, pathologically proven, disease, if patient is under 60 and if disease is not bulky;
- 2) it is part of the whole treatment as prophylactic irradiation of CNS for the lymphoblastic lymphomas and, possibly, for Burkitt type (diffuse non-convoluted small cell);
- 3) it is used for tumors of GI tract removed previously by surgery with no evidence of spread, and followed by chemotherapy;
- 4) it is used in previously bulky disease areas after completion of chemotherapy. Some use it after the first 3 cycles, if the patient achieves remission, followed again by chemotherapy.

The results of treatment for resistant or relapsing patients are poor. Very few patients achieve a long-term remission after relapse or, when failing to respond with an initial aggressive treatment. To salvage these patients there is a multitude of combinations used by various centres. We have tried 2 combinations. One utilizing cis-platinum, VM 26 and hexamethylmelamine and the second cis-platinum and vindesine. Although there were several complete and partial remissions, the duration was short with the exception of 1 patient who is still in remission after 3 years.

In conclusion we can state that:

- 1) CHOP combinations are more effective than the previous ones with a significant number of disease-free long-term survivors. They are easy to use with no severe or lasting toxicity;
- 2) newer combinations, though more toxic, give higher complete remission rates and, probably, long-term survivals in high grade lymphomas. However, their use should be limited to few specialized centres;
- 3) intermediate grade lymphomas have a worse outlook than the high grade ones. More concentrated efforts and more aggressive treatment is needed to improve their outcome. In our opinion, there should not be a distinction between the 2 groups concerning treatment strategies.

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