

INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMAS

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Intermediate and high grade non-Hodgkin's lymphomas are characterized by a biphasic survival curve: A rapidly downsloping curve composed of those patients not achieving durable complete response to initial or salvage therapy, and a plateau representing patients who achieve complete response and durable remission with curative outcome. As curable diseases, it is essential to identify histology accurately, select therapy with the highest potential of durable remission, and remain alert to the secondary effects of treatment that may compromise the quality or durability of survival.

The Working Formulation identifies four intermediate grade histologies (follicular large cell, diffuse small cleaved, diffuse mixed and diffuse large cell lymphoma) and three high grade histologies (immunoblastic, lymphoblastic, and small non-cleaved cell lymphoma). Immunoblastic lymphoma is managed as an intermediate grade lymphoma. Disease entities that have been codified since the Working Formulation and are often considered intermediate grade include: anaplastic large cell lymphoma (ALCL or Ki-1 lymphoma), which must be distinguished morphologically from Hodgkin's disease; and mantle cell lymphoma, a disease without evidence of curative potential utilizing conventional chemotherapy (and therefore, not within the clinical spectrum of intermediate grade survival pattern). Newly recognized, as well, are the lymphomas associated with HIV or HTLV-1 infection. Due to the immunosuppressive effects of viral infection and the aggressive clinical behavior of these lymphomas, treatment recommendations must be considered separately from other non-Hodgkin's lymphomas.

The diagnosis of intermediate or high grade lymphoma is often made on core needle biopsy specimens, as masses may be large, centrally located and accessible by CT guidance. Interpretation of needle aspirates are fraught with imprecision and are not recommended. As all but follicular large cell lymphoma have diffuse nodal architecture, it is less important to assess an entire nodal sample. Nevertheless, it is important to keep in mind that a mixed lymphoma on needle biopsy may be a low grade histology with larger tissue sampling (follicular mixed lymphoma) and that with small fragments it may be difficult to distinguish Ki-1 lymphoma from Hodgkin's disease. Immunophenotyping can be useful on fixed tissue, as can molecular studies of fresh specimens; however, small needle cores may not be fully reliable. It is essential to be confident of the diagnosis before proceeding with therapy as the aim of treatment is a curative outcome.

Staging with CT scans of chest, abdomen and pelvis, gallium scan, and bone marrow biopsy are routine. CSF cytology and prophylaxis for lymphoblastic and small non-cleaved cell lymphoma as well as all bone marrow-involved cases is recommended. The purpose of staging is to identify disease sites for treatment monitoring and to develop a prognostic assessment of outcome which may influence the choice of therapy.

The International Prognostic Index (IPI)⁽¹⁾ is a recently introduced clinical classification incorporating staging and other parameters into a predictive survival model. It is best remembered with the acronym APLES (age, performance status, LDH level, number of extranodal sites and stage). It has been demonstrated to have significant

predictive value in terms of complete response rate, relapse-free survival and overall survival among patients with diffuse mixed, diffuse large cell, and immunoblastic lymphomas. Four prognostic groups are identified: low (87% CR; 70% relapse-free; and 73% overall survival at 5 years), low-intermediate (67%; 50%; 51%), high-intermediate (55%; 49%; 43%), and high risk (44%, 40%, 26%), respectively. Whether the IPI will have validity for all histologic subtypes of non-Hodgkin's lymphomas remains to be clarified.

All patients with intermediate and high grade lymphomas should receive combination chemotherapy. Radiation therapy is often used after chemotherapy when Stage I or II disease is present. The appropriate selection of chemotherapy regimen may be influenced by such factors as expected IPI outcome. For example, low risk patients would be expected to have excellent CR (87%) and overall survival (73%) with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), whereas a high risk patient would fare much worse (44% CR and 26% overall survival). Investigational approaches are certainly valid in the high risk setting.

With the introduction of growth factors and peripheral blood progenitor cell transplantation technology, it is now possible to significantly intensify the initial regimen. It is yet to be determined whether this approach will result in an overall improvement in curative outcome and better survival. Initial intensification exposes all patients to greater acute and potential late toxicities or mortality, and some proportion of such patients would have had a curative outcome with conventional chemotherapy and salvage approaches.

The terminology for dose intensification requires clarification. There are at least four levels of dose intensity: conventional chemotherapy given at ideal dose schedule with growth factor support; conventional chemotherapy administered on a shortened schedule with growth factor support; increased doses of conventional agents with growth factor support only; and myeloablative doses with peripheral blood progenitor cell transplantation. For the sake of discussion, these may be termed levels I-IV.

Levels I and II would be expected to improve acute toxicities but make little impact on curability. Levels III and IV might increase curability but at the expense of toxicity. If second neoplasms or acute mortality are significantly increased over the sequential use of conventional chemotherapy followed by salvage approaches, the cumulative outcome may not favor intensification.

Preliminary data is certainly encouraging that Level III and IV strategies are effective, but longer follow-up and prospective trials will be necessary to conclusively validate these approaches.

Examples of Level III regimens in intermediate grade lymphoma regimens include dose-intense CHOP reported by the Farber Center group⁽²⁾ and NHL-15, a sequential doxorubicin, vincristine, cyclophosphamide regimen, reported by Memorial Sloan-Kettering Cancer Center.⁽³⁾ The CR rate (86% Farber); (75% MSKCC) and relapse-free survival (79% at 20 months; 79% at 24 months) appear improved as compared to CHOP. In the NHL-15 study, the greatest benefit of Level III intensification was in the IPI low-intermediate and high-intermediate risk groups (CR 92%, 83%; overall survival at 2 years 92%, 82%) as compared to CHOP (CR 67%, 55%; overall survival at 2 years 66%, 54%). NHL-15 was not more effective than CHOP in high risk patients (CR 42%; overall

survival at 2 years 46%). The Farber Center data has not been reported separately for dose-intensive CHOP in high risk patients.

Level IV regimens have been utilized as initial therapy in intermediate grade lymphomas, but not routinely reported according to the IPI risk categories. "Poor risk" is not necessarily "high risk" according to IPI criteria. Brugger et al⁽⁴⁾ have reported in abstract excellent results in 20 patients with IPI high risk, aggressive non-Hodgkin's lymphomas. After VACOP-B induction, VIP-E chemotherapy plus G-CSF, peripheral stem cell harvest, and BEAM autotransplant, 19 patients (95%) are in continuous CR at 18 months. These results compare very favorably to the IPI historical experience of conventional chemotherapy.

Gianni et al have reported a prospective comparison of Level IV high dose sequential chemotherapy vs. conventional MACOP-B.^(5,6) Initial results revealed significant improvement in CR (93% vs 63%) and freedom from progression at 21 months (93% vs 48%) but not in overall survival (73% vs. 74%) due to excessive mortality in the Level IV group. Subsequent changes in the Level IV regimen and more selective entry criteria have reduced mortality. However, overall survival is not yet significantly different in the two groups (73% vs. 62% at 43 months).

In lymphoblastic and small non-cleaved cell lymphomas, Level IV strategies have not been employed routinely. Exquisite sensitivity to conventional agents, the frequent presence of circulating cells potentially contaminating the stem cell product and the young patient age making allo-transplant an option at relapse are all factors in limiting Level IV use. Magrath et al⁽⁷⁾ have recently reported impressive results with an alternating regimen administered without growth factor support (CODOX-M: cyclophosphamide, vincristine, doxorubicin, high-dose and intrathecal methotrexate; and IVAC: ifosfamide, etoposide, high-dose cytarabine and intrathecal methotrexate). Of 41 adult and pediatric patients with SNC, 39 achieved CR and event-free survival at 2 years was 92%. GM-CSF did not reduce the duration of neutropenia and significantly prolonged thrombocytopenia in a randomized comparison among high risk patients. Moreover, a severe atypical neuropathy⁽⁸⁾ was described in association with vincristine and growth factor (GM-CSF or G-CSF) therapy.

If the results of this NCI study are confirmed by others, initial curability in high-grade SNCL may be significantly improved without the need for growth factor support or autotransplantation.

For intermediate grade lymphomas, the IPI has delineated the curative limits of conventional chemotherapy. At this time, it appears encouraging that Level III and IV dose intensification may significantly improve curability. Future study will determine the appropriate application of these new dose-intensive strategies.

References

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