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The importance of follow-up biopsies of clinically suspicious lymphadenopathy in nodular lymphocyte predominant Hodgkin's lymphoma

Although nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) is an indolent disorder, clinically suspicious lymphadenopathy commonly develops during follow-up. In our series of 100 cases of NLPHL, fifteen cases with sequential biopsies were identified. The vast majority showed reactive changes only, emphasizing the importance of histologic sampling of lymphadenopathy in NLPHL patients.

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Nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) is a rare disorder, characterized by a proliferation of isolated large atypical cells embedded in a B-cell rich stromal infiltrate. Lymphadenopathy, a phenomenon that is commonly observed during follow-up in NLPHL patients, may indicate recurrence or signal disease progression to a diffuse large B-cell lymphoma (DLBCL).

A total of 105 NLPHL cases were retrieved from the records of the Department of Pathology of the University Hospitals of the K.U. Leuven. All cases had been diagnosed in the period between September 1990 and December 2001 and consistently followed up by the clinicians of the same institution. In 15 of the 100 confirmed cases of NLPHL, additional biopsies were available (27 biopsies in total), taken either before the diagnosis of NLPHL was established or during the course of the disease.

In fifteen out of 100 patients in whom the diagnosis of NLPHL was confirmed, clinically suspicious enlarged lymph nodes occurred during the course of their disease. Importantly, neither the morphologic nor the immunophenotypic features of the NLPHL observed in these patients were in any respect distinguishable from those in patients who did not develop lymphadenopathy. Four of these 15 patients had a recurrence of NLPHL, and in three patients a DLBCL was found. In ten patients, sequential lymph node biopsies revealed non-specific lymphadenitis with or without progressive transformation of germinal centers.

NLPHL is generally assumed to be an indolent disease, but despite the overall excellent prognosis, disease recurrence has been noted relatively frequently.[1-3] This paradox has been explained by the fact that the relapses typically respond well to treatment. However, important lymphadenopathy occurring in a lymphoma patient is often considered to be a relapse without histopathological confirmation. Indeed, we have found no more than five patients in whom NLPHL relapsed. Only two of these patients experienced multiple relapses. Moreover, several large studies have failed to confirm the classically described pattern of frequent and multiple relapses.[2-3] Hence it is likely that NLPHL is essentially a curable disease in which relapses are only occasionally observed.

Long-term survivors of all subtypes of Hodgkin's lymphomas are at risk of late complications, in particular the developmment of various types of solid tumors, acute leukemia and non-Hodgkin's lymphoma (NHL).[4] Hardly any study on the risk of a second cancer in Hodgkin's lymphoma has been sufficiently large to allow meaningful subgroup analyses with respect to the risk of developing NHL. The few surveys that attempted this analysis demonstrated that the relative risk of NHL was significantly higher for NLPHL patients than for patients with other subtypes of lymphoma, with a reported incidence of 2-10% depending on the stringency of the histology review and the duration of follow-up.[5-7] We found that NLPHL and DLBCL were associated in 3 out of the 100 patients.

Based on a limited number of cases, it has previously been assumed that DLBCL associated with NLPHL has an excellent prognosis, better than that for *de novo* DLBCL.[8] Yet, in all three of our cases with this association, the occurrence of DLBCL precipitated a fulminant downhill clinical course, as reported in several large scale clinical studies.[1-3,5]

Occasionally, the DLBCL arising in a context of NLPHL have been described to show features of T-cell histiocyte-rich B-cell lymphoma (THR-BCL). Based on a number of morphologic and clinical similarities, including the cytological features of the neoplastic cells, their B-cell phenotype, male preponderance, age distribution, and the tendency to transform to a stroma-poor DLBCL, it was proposed that THR-BCL might represent a transformed NLPHL.[9] However, not a single case of NLPHL-associated THR-BCL was identified in our series, underscoring the rarity of histologic progression of NLPHL into THR-BCL.

Our results, like those reported by the European Task Force on Lymphoma,[1] confirm the overall favorable outcome of NLPHL, even in patients who show clinical evidence of recurrence. Yet the good-to-excellent prognosis of the latter patients, which has been ascribed previously to the presumed intrinsically indolent character of relapse, may be explained in part by the fact that clinically suspicious enlarged lymph nodes often show only reactive changes. Occasionally, however, a proliferation that is morphologically recognized as a DLBCL develops on the background of NLPHL. Our findings demonstrate that, contrary to what has been previously suggested, in this context the latter may follow a highly aggressive course, compelling intensive treatment. Hence, apart from its utility in avoiding over-treatment of cases of reactive hyperplasia, biopsies of any clinically suspicious lymphadenopathy is essential in order to prevent under-treatment which may compromise the outcome of cases of NLPHL-associated DLBCL.

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Thalidomide plus oral melphalan for advanced multiple myeloma: a phase II study

Thalidomide exerts synergistic or additive effects when combined with other drugs. This study reports the toxicity and efficacy of the combination of thalidomide plus oral melphalan in 27 patients with advanced multiple myeloma. We found that this combination induces a high response rate and a long progression-free survival without significantly increasing thalidomide-related toxicity.

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There are few therapeutic options available for patients with relapsed-refractory multiple myeloma (MM). Since the first report by Singhal *et al*.,[1] attention was focused on thalidomide or thalidomide combined with dexamethasone or chemotherapy. Unfortunately, there was a significant increase in side effects, mainly deep venous thrombosis and myelosuppression, in association with combination therapy.[2,3] We report our experience using thalidomide and oral melphalan in patients with advanced MM.

From May 2000 to July 2002 in our tertiary care institute and in the main medical institutions of the Marche region (Italy) 27 patients with relapsed-resistant MM were treated with thalidomide plus melphalan. Patients with poor performance status and/or cardiopulmonary, renal and liver diseases were not excluded whereas patients with severe mental disorders or severe peripheral or central neuropathy were not enrolled. All patients signed a written informed consent form. The starting dose of thalidomide was planned to be 100 mg p.o. daily at bedtime, escalated weekly by 100 mg increments up to a maximum dose of 600 mg, in the absence of severe side effects. Thalidomide was stopped only because of severe side effects or disease progression. Melphalan was administered intermittently at a dose of 0.20 mg/kg/day p.o. for four days every 28 days for at least one course after greatest response was achieved or until severe toxicity developed. No patients received antithrombotic prophylaxis. Responses to therapy were assessed as reductions of paraprotein in serum and/or urine of at least 25%, 50% and 75% without the appearance of new skeletal lesions or an increase in bone marrow plasma cells. Complete response (CR) was defined according to EBMTR/IBMTR criteria.[4] Toxicity was assessed according to the Word Health Organization (WHO) criteria.

Forty percent of patients were aged >70 years; more than 2 prior regimens had been administered to 56%, prior high-dose therapy with stem cell support to 41% and prior therapy with melphalan to 96% of patients β2-microglobulin concentration was > 3 mg/L in 63% and the disease had been present for longer than 3 years in 30% of patients.

Paraprotein decreases of ≥ 50% and ≥ 75% were obtained in 59% and 15% of patients, respectively (Table 1). Remarkably, 3 out of 4 patients who had a maximal response had no monoclonal paraprotein detectable by immunofixation. The median time to remission was 6 weeks. The main side effects were constipation (82%), somnolence (41%), fatigue (22%), sensory peripheral neuropathy (56%), deep venous thrombosis (11%) and grade 3 leukopenia (30%). However, no severe infections occurred. After a median follow-up of 15 months (range 6-32), 9 patients (33%) had disease progression and 6 (22%) had died. The 2-year progression-free survival (PFS) and overall survival (OS) were both 61%.

As a single agent thalidomide produces an overall response rate of 30% and a 2-year event-free survival (EFS) of 20% in patients with heavily pretreated MM. Some studies have demonstrated that thalidomide may restore the sensitivity of myeloma cells to apoptosis induced by drugs, preventing the interaction between tumor cells and stromal cells.[5,6] We found