Hematological Oncology
Hematol Oncol 2013; **31** (Suppl. 1): 47–50
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2067

Supplement Article

VII. Management of nodular lymphocyte-predominant Hodgkin lymphoma

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Keywords: **nodular lymphocyte-predominant Hodgkin lymphoma; radiotherapy; chemotherapy; immunotherapy**

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) accounts for about 5% of all Hodgkin lymphoma (HL) cases [1]. This entity differs substantially from the histological subtypes of classical HL (cHL) in terms of immunohistology, clinical presentation, and course. The B-cell marker CD20 that is only inconsistently found on Hodgkin and Reed–Sternberg cells in cHL represents a hallmark of the disease-defining lymphocyte-predominant (LP) cells. In contrast, LP cells usually lack the CD30 and CD15 antigens that are typically expressed on Hodgkin and Reed–Sternberg cells (Figure 1; Table 1) [2]. The majority of NLPHL patients are diagnosed with early favourable stages. These patients have a very good prognosis and long-term remission is achieved in more than 90% of cases. In more advanced NLPHL, particularly late relapses are frequently observed. However, most relapses can be salvaged successfully resulting in an excellent overall survival (OS) for NLPHL patients [3].

First-line treatment of nodular lymphocyte-predominant Hodgkin lymphoma

Treatment of early favourable stages

Most NLPHL cases are diagnosed with early favourable stages, that is, stage I/II disease without B-symptoms or clinical risk factors. Except for stage IA, the standard of care for early favourable stages is very similar to cHL consisting of a brief chemotherapy followed by involved-field radiotherapy (IF-RT). Patients diagnosed with stage IA NLPHL are sufficiently treated with IF-RT alone as shown by analyses from different groups [4,5].

A study from the German Hodgkin Study Group (GHSG) retrospectively compared IF-RT, extended-field RT (EF-RT), and combined-modality treatment (CMT) in patients with stage IA NLPHL. A total of 131 patients (45 EF-RT, 45 IF-RT and 41 CMT) were included in the analysis. Complete remission (CR) was achieved in 99% of cases (98% after EF-RT, 98% after IF-RT and 100% after CMT). Freedom from treatment failure (FFTF) rates at 24 months were 100% for EF-RT, 92% for IF-RT and 97% for CMT with no significant differences between the treatment approaches; OS rates at a median follow-up of 78 months for EF-RT, 17 months for IF-RT and 40 months for CMT were 94%, 100% and 96%, respectively. Treatment-related toxicity was more common among patients who had CMT (48.8% grade III/IV toxicity) in comparison with EF-RT (2.2% grade III/IV toxicity) and IF-RT (2.2% grade III/IV toxicity) [4].

A recent publication from the USA reported the long-term course of 113 patients with stage I/II NLPHL treated with RT alone ($n = 93$), CMT approaches ($n = 13$) or chemotherapy alone ($n = 7$). After a median observation of 136 months among survivors, patients treated with RT alone had an excellent outcome. Results could not be further improved by the addition of chemotherapy. Chemotherapy alone was associated with an increased relapse rate. The extent of RT could be safely reduced from EF-RT to IF-RT without compromising treatment results. Secondary malignancies and cardiovascular disease were less frequent after IF-RT when compared with EF-RT. Patients with stage I disease had a superior progression-free survival (PFS) in comparison with stage II patients. However, this advantage in PFS did not translate into a better OS [5].

With the aim to reduce the risk of late effects associated with chemotherapy and RT, a prospective GHSG phase II study evaluated the possible role of the anti-CD20 antibody rituximab as single agent in 28 patients with newly diagnosed stage IA NLPHL. The response rate after four weekly doses of 375 mg/m^2 was 100%. However, after a median follow-up of 43 months, 25% of patients had relapsed so that this approach appeared to be associated with an inferior tumour control as compared with RT alone or CMT. Thus, it was not adopted as novel standard of care for patients with stage IA NLPHL [6].

For NLPHL patients with early favourable stages other than stage IA, CMT approaches may represent the most

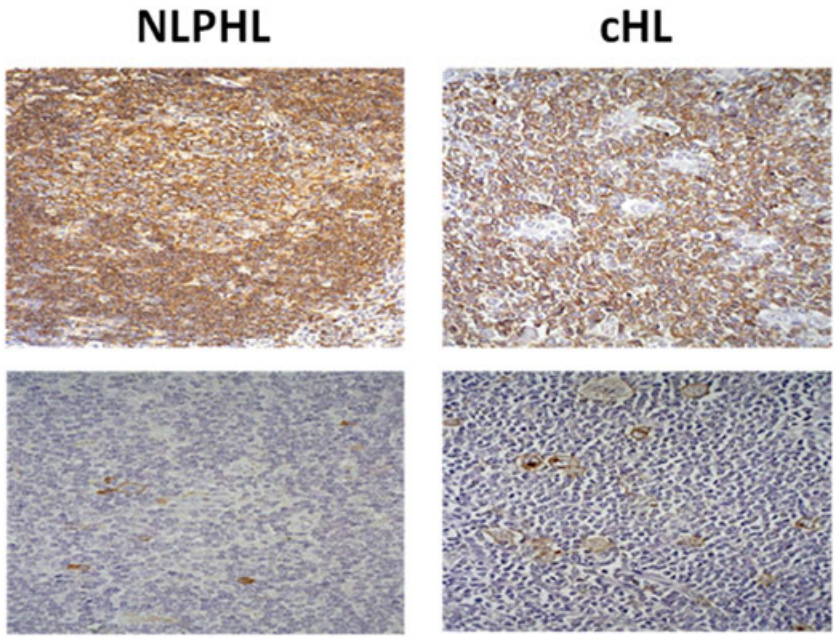

Figure 1. CD20 (above) and CD30 (below) staining in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL) (lymphocyte-rich subtype)

Table 1. Staining characteristics of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL)

	NLPHL	cHL
CD15	–	+
CD20	+	±
CD30	–	+
CD45	+	–
EMA	+	–

EMA, epithelial membrane antigen.

suitable treatment. A Canadian study including a total of 88 NLPHL patients with early favourable stages retrospectively compared the outcome of 32 patients treated with RT alone between 1966 and 1993 with the outcome of 56 patients treated with CMT approaches between 1993 and 2009. As a major finding, the study revealed a significantly better PFS for patients treated with CMT approaches [7]. Although this analysis has some limitations and results have to be interpreted with caution as patients were treated over a period of more than four decades, the improved tumour control with CMT approaches should be kept in mind when choosing treatment for patients with NLPHL in early favourable stages other than stage IA.

Treatment of early unfavourable and advanced stages

Treatment of NLPHL patients presenting with early unfavourable and advanced stages is usually very similar to cHL. It consists mainly of CMT approaches for early unfavourable stages and six to eight cycles of chemotherapy followed by localized RT to larger residual disease for advanced stages. The chemotherapy protocols most often applied include ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbzine, and prednisone). As shown by a comprehensive analysis from the GHSG comprising 394 NLPHL patients and 7904 cHL patients, treatment results for both histologies were comparable when using these regimens. At 50 months, FFTF rates for patients with NLPHL and cHL diagnosed with early unfavourable stages were 87% and 85%, respectively. Patients with advanced stages had FFTF rates of 77% and 75% when diagnosed with NLPHL and cHL, respectively [3]. More recently, retrospective data on the use of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone) in NLPHL have become available. A total of 15 patients (4 stage I/II patients and 11 stage III/IV patients) were treated with this protocol at a single institution. Response rate was 100%. At a median follow-up of 42 months, no patient had relapsed. However, results from prospective studies confirming these promising results are pending [8].

Diagnosis and treatment of relapsed nodular lymphocyte-predominant Hodgkin lymphoma

Risk of transformation into aggressive B-cell non-Hodgkin lymphoma

Patients initially treated for more advanced NLPHL tend to have late relapses. Therefore, long-term follow-up is

DOI: 10.1002/hon

necessary. If relapse is clinically suspected, diagnostic lymphadenectomy should be performed whenever possible. This is due to an increased risk of transformation from NLPHL into aggressive B-cell non-Hodgkin lymphoma (B-NHL). Here, T-cell-rich B-NHL is the most often diagnosed histology. Two recent analyses addressing this issue revealed transformation rates exceeding those previously reported. A French study including 164 patients indicated a 10-year transformation rate of 12% [9]. According to a Canadian study comprising 95 patients, the actuarial risk of transformation was 7% at 10 years and 30% at 20 years [10]. In both studies, transformation into aggressive B-NHL was associated with an impaired prognosis.

Treatment of relapsed nodular lymphocyte-predominant Hodgkin lymphoma

Standard treatment for histologically proven relapsed NLPHL is ill-defined. Some studies indicate that high-dose chemotherapy followed by autologous stem cell transplantation (ASCT)—the standard of care for relapsed cHL - may not be the appropriate treatment for most patients with relapsed NLPHL. This is particularly true for patients with low tumour burden and slow disease progression.

One study retrospectively analyzing the use of high-dose chemotherapy followed by ASCT in relapsed NLPHL included 19 patients that had been transplanted between 1987 and 2002. At 5 years, PFS and OS rates were 39% and 53%, respectively, and thus not very promising given the excellent long-term survival rates reported for NLPHL even after relapse [11]. Additional data on the value of high-dose chemotherapy followed by ASCT in patients with relapsed NLPHL came from the UK. The outcome of a total of 88 NLPHL patients treated at a single institution over a period of three decades was reported. Eight of these patients had had high-dose chemotherapy and ASCT at first or higher grade of relapse. With a median failure-free survival of 39.2 months, five patients relapsed again and required additional salvage treatment, whereas three patients remained in remission [12].

The anti-CD20 antibody rituximab was prospectively evaluated by different groups in relapsed NLPHL. The Stanford group conducted a study including 12 patients with newly diagnosed NLPHL and 10 patients with relapsed disease. After four weekly standard doses of rituximab at 375 mg/m^2, response rate was 100%. However, at a median follow-up of 13 months for the whole patient group, disease recurrence was seen in three of the 10 patients that had already received treatment prior to study entry [13]. Results from a phase II study conducted by the GHSG including 15 patients with relapsed NLPHL were similar. An overall response rate of 94% was observed after four weekly standard doses of rituximab. At 63 months, the median time to progression was

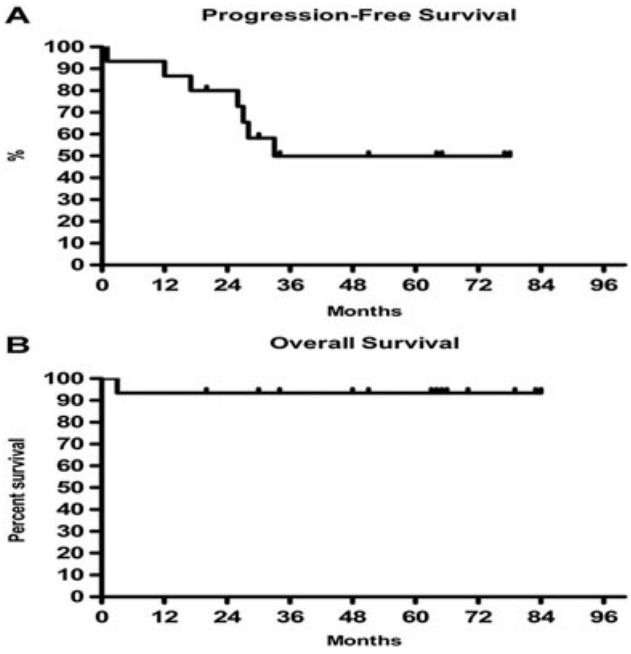

Figure 2. Progression-free survival and overall survival of relapsed nodular lymphocyte-predominant Hodgkin lymphoma patients treated with rituximab (adopted from [14])

33 months, the median OS was not reached (Figure 2). Only one patient had died [14]. The antibody was well tolerated in both studies. Thus, given the relevant toxicity and the potentially reduced efficacy of high-dose chemotherapy followed by ASCT in relapsed NLPHL on the one hand and the good tolerability and the excellent response rates observed with rituximab on the other hand, anti-CD20 antibody treatment with rituximab or follow-up products represents a reasonable choice for the majority of patients with relapsed NLPHL.

Future strategies in nodular lymphocyte-predominant Hodgkin lymphoma

At present, many NLPHL patients do not die from their lymphoma but from treatment-related late effects such as cardiac failure and secondary malignancies. Thus, the major goal of future treatment strategies will consist in reducing acute and particularly late toxicity without compromising efficacy. This could at least in part be achieved by implementing anti-CD20 antibodies into the standard protocols currently used for the first-line treatment of NLPHL. In return, it might become possible to reduce or even omit more toxic conventional chemotherapeutics contained in these regimens. Unfortunately, results from prospective clinical trials addressing this issue are pending. Besides chemotherapy and immunotherapy, RT could also be subject to further optimization. Radiation fields and doses might still be further reduced. In this context, a joint group from France and

DOI: 10.1002/hon

the Netherlands reported the outcome of nine NLPHL patients treated with 4 Gy IF-RT alone. Response rate was 89%. No relevant toxicity was observed. However, at a median follow-up of 37 months, five patients had developed local relapse [15]. Thus, further efforts to improve the risk-benefit ratio of RT in the treatment of NLPHL are necessary. In relapsed NLPHL, more prospective and retrospective analyses on the role of high-dose chemotherapy followed by ASCT as well as the ultimate value of anti-CD20 antibodies are required to draw final conclusions and define a standard of care. Thus, the GHSG currently evaluates the fully human anti-CD20 antibody ofatumumab in a prospective phase II study including patients with histologically proven relapsed NLPHL (NCT01187303). Besides anti-CD20 antibodies, further targeted treatment strategies appear worth being tested in NLPHL. For instance, the Bruton tyrosine kinase inhibitor ibrutinib that has shown promising activity in some NHL entities such as mantle cell lymphoma and chronic lymphocytic leukaemia may also be effective in NLPHL given the clinical and biological properties of NLPHL often resembling indolent NHL [16].

Conflict of interest

The authors have no competing interest.

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DOI: 10.1002/hon