Rituximab in a risk-adapted treatment strategy gives excellent therapeutic results in nodular lymphocyte-predominant Hodgkin lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma (NLP-HL) is a rare variant of Hodgkin lymphoma, histologically characterized by prominent lymphocytic proliferation mixed with histiocytes that form at least a partially nodular pattern. Due to its rarity, this type of lymphoma still lacks consolidated and widely accepted treatment guidelines. Current first-line therapy approaches are often based on radiotherapy (RT) alone for non-bulky early-stage NLP-HL, while chemotherapy regimens [ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)] plus RT have been widely used for the most advanced stages (Eichenauer *et al*, 2014; Hoppe *et al*, 2015). The observation that malignant lymphocytes of NLP-HL, although negative for CD15 and CD30, consistently express CD20 (Hartmann *et al*, 2014), provides the rationale for the inclusion of anti-CD20 antibody rituximab in the treatment of this disease as a low toxic component for replacing chemotherapy and/or RT.

Therefore, the outcome and side effects of 12 consecutive patients with newly diagnosed NLP-HL, who were treated in our Institution using a risk-adapted, rituximab-based protocol, were compared with those of a historical cohort of NLP-HL patients, previously treated with a conventional modality approach, i.e. chemotherapy and/or RT (Table I). The clinical features of these two groups of patients were similar(see Supplementary data), except that the rituximab group presented more sub-diaphragmatic disease ($P = 0{\cdot}01$) and the historical cohort included more patients with bulky disease ($P = 0{\cdot}03$), thus balancing adverse prognostic factors (see Table SI). All 24 patients showed the typical CD20 positive stain in at least 30% of tumour cells without either CD15 or CD30 reactivity (Swerdlow *et al*, 2008). Comparing the treatments in the two series, 9 historical patients, and no patients of the rituximab group, underwent involved-field (IF)RT; cytotoxic agent administration was spared in 42% of the patients of the rituximab group (Table I). At final restaging, 23 of the 24 patients (95·8%) were in complete remission [CR; (Cheson *et al*, 2007)], while one historical patient showed refractory disease and was underwent rescue therapy. Patients who received rituximab-based risk-adjusted therapy showed excellent response to the treatment and had better progression-free survival (PFS, $P = 0{\cdot}04$) but not overall survival (OS) than those of the historical cohort (see Figure S1). Indeed, during follow-up (median 4·3 years; range, 0·5–8·2 in the whole cohort), four patients, all belonging to the historical cohort and treated with ABVD ± IFRT, showed refractory ($n = 1$) or recurrent disease ($n = 3$). These results confirm that NLP-HL, despite a more indolent clinical behaviour than classical HL, may show late multiple relapses after conventional therapy particularly in advanced stage patients. Therefore, there is a need for novel treatment approaches that, along with low toxicity, have an increased efficacy to improve the overall prognosis.

In our more recent series of NLP-HL patients, the use of rituximab as single agent in the induction phase was restricted only to stage I and II patients without risk factors. However, in order to minimize the possibility of relapses, we prolonged the anti-CD20 antibody treatment, with eight further infusions (once every 3 months) distributed over a 2-year maintenance therapy in these patients with early favourable disease. Therefore, as seen in indolent non-Hodgkin lymphoma, the use of rituximab-maintenance in early favourable NLP-HL seems to delay or avoid relapse. In the remaining patients, according to a risk-adapted treatment approach, rituximab therapy was combined with polychemotherapy, giving a total of four cycles of ABVD to patients with stages I or II disease but with ≥1 risk factors (early unfavourable) and six cycles of ABVD to those who presented with advanced stages (Fig 1). Importantly, the inclusion of rituximab in this therapeutic scheme appears to provide long-term protection from relapse when compared with the classical chemo-radiotherapy. Notably, we observed a higher rate of grade 3–4 neutropenia in the historical cohort (54%) than the rituximab group (10%; $P = 0{\cdot}009$); non-haematological toxicity was recorded only in the historical cohort and was prevalently RT-related (4/8 thyroid disease, 2/8 lung fibrosis and 2/8 osteoarthritic degeneration). Over the study period, one patient died due to bleomycin-induced pneumonitis following the last cycle of R-ABVD. These results underscore the role of anti-CD20 antibody in NLP-HL, which provides substantial benefit to many patients, avoiding the need for RT and cytotoxic agent treatment or, at least, potentially delaying the need for both, in those with early favourable stage disease. In the recent study by Advani *et al* (2014), rituximab was given as single agent once per week for 4 weeks to early-stage NLP-HL patients, giving an overall response rate (ORR) of 100% with a 67% CR rate. The last 16 patients also had received a maintenance phase with rituximab (MR) once per week for

Table I. Response to treatment.

		Historical Cohort ABVD ± RT (n = 12)			Rituximab Group R ± ABVD (n = 12)		
	Overall (n = 24)	Early favourable (n = 4)	Early unfavourable (n = 5)	Advanced (n = 3)	Early favourable (n = 5)	Early unfavourable (n = 2)	Advanced (n = 5)
Therapy*							
ABVD		4 cycles	4 cycles	6 cycles	–	4 cycles	6 cycles
IFRT		30 Gy	30 Gy	–	–	–	–
Rituximab		–	–	–	Induction (4 weeks) + maintenance (2 years)	Induction (4 months)	Induction (6 months)
Response, n							
Complete remission	23	4	5	2	5	2	5
Partial response	–	–	–		–	–	–
Refractory disease	1	–	–	1	–	–	–
Tumour events, n							
HL relapse	3	1	–	2	–	–	–
Survival analysis							
Median F-U, months (range)	51 (6–98)	67 (48–98)	68 (47–84)	25 (12–36)	46 (36–68)	63 (43–83)	51 (6–96)
Progression-free survival, n							
At 2 years		4	5	1	5	2	5
At 5 years		4	5	–	5	2	5
Overall survival at last F-U, n		4	5	3	5	2	4

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; F-U: follow-up; HL, Hodgkin lymphoma; IFRT, involved field radiotherapy; R, rituximab; RT, radiotherapy.
*Detailed description of patient therapy is given in Fig 1 and the supplemental data.

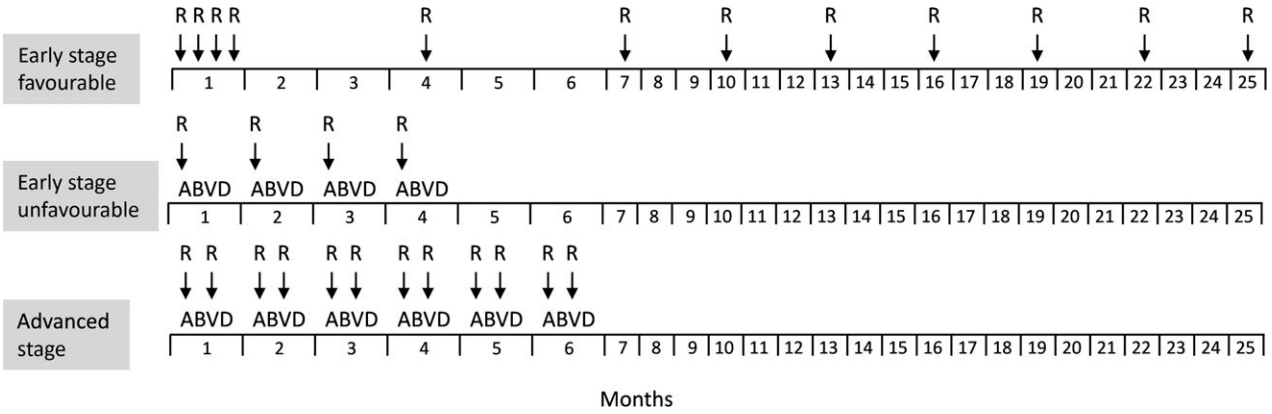

Fig 1. Scheme of risk-adapted, rituximab-based protocol used in the most recently treated patients with newly diagnosed Nodular lymphocyte-predominant Hodgkin lymphoma ($n = 12$). The five patients with early favourable disease, i.e. Stage I or II without risk factors, received an induction treatment consisting of four weekly administrations of rituximab (375 mg/m^2 i.v.), followed by a 2-year maintenance phase in which rituximab (375 mg/m^2 i.v.) was administered once every 3 months. The two patients with early unfavourable stage, i.e. Stage I or II with at least one risk factor, were treated with rituximab (375 mg/m^2 i.v. once per month for four consecutive months, on day 1, plus 4 cycles of ABVD). The remaining five patients with advanced stage (Stage III or IV) received rituximab (twice per month, on days 1 and 15, for 6 consecutive months; 375 mg/m^2 i.v.) plus 6 cycles of ABVD. ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; R, rituximab.

4 weeks every 6 months for 2 years (R + MR). In previously untreated patients, the median PFS for the R and R + MR regimens was 1·9 and 5·6 years, respectively; progression occurred in 8 of 12 patients treated with R and in 5 of 9 patients treated with R + MR (Advani *et al*, 2014). In this trial, however, the early-stage group also included those patients with risk factors (Eich *et al*, 2010).

Our results underline the importance of therapy stratification on the basis of risk at baseline and indicate that patients with risk factors deserve chemotherapy while, for those patients with very limited stage disease, prolonged exposure to rituximab is sufficient to guarantee long lasting protection against disease recurrence. Indeed, when therapy with rituximab as single agent was given in only four weekly doses within 1 month, despite an initial impressive ORR of 100% with CR observed in 24 of the 28 patients, short rituximab exposure appears to be insufficient to preclude the likelihood of continuous early relapses as indicated by PFS rates of 96·4%, 85·3% and 81·4% at 12, 24 and 36 months, respectively and 25% of total disease recurrences observed in the study (Eichenauer *et al*, 2015).

In conclusion, front-line rituximab treatment when followed by a 2-year maintenance therapy seems to have a low toxicity and a high efficacy in treating patients with early stage NLP-HL without risk factors, replacing chemotherapy and/or RT schemes. Furthermore, the combination of anti-CD20 antibody with the classical ABVD schedule within a risk-adjusted treatment strategy may be used in the therapeutic approach of patients with NLP-HL with more advanced stages, sparing toxicity derived from the use of RT.

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RDP, MP and FP designed the study, analysed the data and wrote the manuscript draft. CG, IZ, MR and MDP collected the data for the statistical analysis. Statistical analysis was performed by NP and CC. GT and GC confirmed all histological diagnosis of NLP-HL. MP, MI and FP critically reviewed the manuscript drafts, approved the final version and made the decision to submit the manuscript for publication.

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Fig S1. Kaplan-Meier curves of progression-free survival per treatment schedule.

Table SI. Patient and tumor characteristics.

Data S1. Supplementary data.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

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Clinicopathological characteristics, outcomes and pattern of mutations in patients with follicular lymphoma who progressed on Bruton tyrosine kinase inhibitors

Ibrutinib and acalabrutinib (Byrd *et al*, 2015) are Bruton tyrosine kinase (BTK) inhibitors (BTKi) that have revolutionized the treatment of patients with different lymphoid cancers. The survival of patients with lymphoid cancers who progressed after ibrutinib therapy is poor (Jain *et al*, 2015; Martin *et al*, 2016) and is dependent upon disease characteristics and the cause of discontinuation. However, the survival of patients with follicular lymphoma (FL) after discontinuing BTKi has never been reported. Mechanisms of ibrutinib resistance are under exploration (Ahn *et al*, 2017). C481S, T474I and L528W mutations in *BTK* and activating mutations in phospholipase-gamma-2 (*PLCG2*) are considered to be primary mechanisms of ibrutinib resistance (Chiron *et al*, 2014; Burger *et al*, 2016). It remains unknown whether patients with FL who progress on BTKi therapy also exhibit BTK mutations, although recurrent mutations in the B cell receptor signalling pathway, upstream of BTK, have been reported in patients with FL (Krysiak *et al*, 2017).

We evaluated the characteristics and the pattern of mutations in patients with FL who progressed on BTKi by analysing patients with FL enrolled in clinical trials with BTKi at our institution between 2013 and 2016. Of 60 patients we