

# Recent therapeutic advances in hematological malignancies: the role of targeted therapies in lymphoma

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## introduction

Destruction of tumor cells by tackling of tumor-specific surface or intracellular properties and thus sparing normal tissues remains the ultimate goal of tumor therapy. Although none of the therapies available today completely match these requirements a number of new treatment modalities are getting closer to achieving this goal.

In lymphoma, monoclonal antibodies binding to antigens specific to lymphocytes in different stages of maturation have dramatically changed treatment algorithms. Although many more antibodies have been tested, only antibodies binding to the CD20 antigen on B cells and the CD52 antigen on T-cells are broadly used in the clinic. Antibodies against other B-cell antigens like CD22, CD19 or CD37 or antibodies against CD3, CD4 or CD8 on T-cells are not widely used in the treatment of lymphoma in 2008.

The chimeric anti-CD20 human immunoglobulin G1 monoclonal antibody rituximab is the antibody which is almost exclusively used to treat patients with B-cell lymphoma. While the next generation of naked anti-CD20 antibodies is already under study [1] radio-labeled anti-CD20 antibodies like [<sup>90</sup>Y]ibritumomab–tiuxetan (Zevalin) or [<sup>131</sup>I]tositumomab (Bexxar) have been made available to oncologists and may represent another step forward in successfully treating patients with B-cell lymphomas who previously failed rituximab or who are ineligible for more aggressive therapy.

## aggressive lymphoma

### radio-immunotherapy

Radio-immunotherapy has no established role in aggressive lymphoma. In patients with relapsed diffuse large B-cell lymphoma (DLBCL) a recent study demonstrated that single agent [<sup>90</sup>Y]ibritumomab–tiuxetan can induce further remissions. However, while the overall response rate (ORR) was 53% in rituximab-naïve patients, it was only 19% in patients pretreated with rituximab [complete remission (CR)/complete remission unconfirmed (CRu) rate 12%] [2]. These data demonstrate that the efficacy of radio-labeled anti-CD20 antibodies is highly dependent on previous therapy with the naked antibody. Only a head-to-head comparison of a

radio-labeled and a naked antibody in a prospective, randomized study will ultimately show whether there is a role for [<sup>90</sup>Y]ibritumomab–tiuxetan or [<sup>131</sup>I]tositumomab in patients with aggressive lymphoma. Such studies are ongoing. It should be mentioned that new radio-immunoconjugates are being developed and animal experiments have shown promising results [3].

### first-line therapy including rituximab

A number of prospective, randomized, phase III studies have shown that the addition of rituximab to cyclophosphamide–adriamycin–vincristine–prednisone (CHOP) significantly improves the outcome of patients with DLBCL. The first study was reported by Coiffier et al. [4] and was updated recently [5]. The French study group Groupe d'Etude des Lymphomes de l'Adulte (GELA) treated 399 patients aged 60–80 years with eight courses of CHOP-21 or R-CHOP-21 (time interval between treatment courses was 21 days). The 7-year progression-free survival (PFS) was 52% for R-CHOP and 29% for CHOP ( $P < 0.0001$ ), overall survival (OS) was 53% for R-CHOP versus 36% for CHOP ( $P = 0.0004$ ). Benefit was observed in patients with low-risk and high-risk International Prognostic Index (IPI).

The recently published RICOVER-60 study by the German High-grade Lymphoma Study Group (DSHNHL) treated elderly patients with aggressive B-cell lymphomas, mostly DLBCL, using either six or eight courses of CHOP-14 or R-CHOP-14 (time interval between treatment courses 14 days). The best results were obtained with six courses of R-CHOP-14. The 3-year event-free survival (EFS) rate and OS rate were 67% and 78%, respectively, and proved significantly better than the EFS and OS observed after six courses of CHOP-14 or eight courses of CHOP-14 or R-CHOP-14 [6].

Other studies like the US Intergroup/Eastern Cooperative Oncology Group (ECOG) trial [7] or the HOVON trial [8] also showed that the addition of rituximab to CHOP-21 or CHOP-14 significantly improves the outcome for elderly patients (>60 years) with aggressive B-cell lymphomas.

In younger patients with good-risk DLBCL the MInT (Mabthera International Trial) study demonstrated that the addition of rituximab to six courses of CHOP or CHOP-like chemotherapy significantly improved EFS and OS. At a median

follow-up of 34 months patients treated with CHOP-like therapy and rituximab had a 3-year EFS of 79% compared with 59% in patients treated with chemotherapy alone ( $P < 0.0001$ ). OS was increased from 84% to 93% in patients given rituximab ( $P = 0.0001$ ). This study for the first time in the history of lymphoma therapy showed a 100% 3-year OS in the favorable subgroup of patients (IPI 0, no bulky disease) treated with R-CHOP-21 [9].

There is no study to date formally demonstrating an advantage of the addition of rituximab to chemotherapy in young, high-risk patients [age-adjusted IPI (aaIPI) 2 and 3] with DLBCL. This is largely due to the fact that most study groups use high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) in these patients. The addition of rituximab to HDT/ASCT is feasible and safe with high rates of CR and good EFS and OS [10].

### relapsed disease and rituximab

Single-agent activity of rituximab in patients with relapsed DLBCL was first shown by Coiffier in 1998 [11]. A number of phase II studies have demonstrated that rituximab could safely be combined with salvage chemotherapy like the iphosphamide–carboplatin–etoposide (ICE) or cisplatin–cytarabine–dexamethasone (DHAP) regimen [12, 13].

Currently, a randomized phase III study comparing R-DHAP with R-ICE followed by carmustine–cytarabine–etoposide–melphalan (BEAM) HDT and ASCT is about to be closed [14]. This study is important because for the first time two salvage regimens have been compared head-to-head; additionally, patients are randomized to rituximab maintenance or observation following HDT/ASCT. Thus, the role of maintenance therapy in patients with relapsed DLBCL who achieve a remission after HDT/ASCT will be clarified.

## follicular lymphoma

### first-line therapy including rituximab

The addition of rituximab to the previously known therapeutic options may for the first time alter the clinical course of patients with follicular lymphoma (FL) and some patients hopefully will be cured or at least enjoy long-lasting remission. In contrast to the situation in aggressive lymphoma, the situation in FL is much more complex because rituximab may be used as single agent or together with mono- or combination chemotherapy. Furthermore, maintenance therapy with rituximab after any of these treatments may further improve treatment outcome.

Several groups investigated the use of rituximab as front-line therapy for FL [15–19]. The ORR was in the order of 75% with almost half of these patients achieving CR. Most patients, however, progressed between 1 and 2 years after initial therapy and needed re-treatment. In order to prevent or postpone relapse several strategies have been proposed. At this time, it is not yet clear whether prolonged treatment with rituximab as proposed by the Swiss SAKK group [18] or re-treatment at the time of relapse [16] will ultimately yield the best results. Randomized phase III studies comparing these strategies are ongoing.

At least four randomized studies have addresses the question of whether the addition of rituximab to various chemotherapy protocols improves PFS and/or OS. These studies all demonstrated a significant improvement of PFS and OS when rituximab was added to chemotherapy. However, different chemotherapies were used, and consolidation/maintenance therapy included a variety of modalities [interferon (IFN) combined with cyclophosphamide–doxorubicin–vindesine–prednisone (CHVP), consolidation with HDT/ASCT, rituximab maintenance] (Table 1). Therefore, it is not possible

**Table 1.** Randomized studies in patients with follicular lymphoma using rituximab plus chemotherapy

Study	Treatment, <i>n</i>	Median <i>f/u</i> in months	ORR (%)	CR (%)	Median TTF (months)	OS (%)
Marcus et al., 2006 [20, 21]	CVP, 159R-CVP, 162	53	5781	10 41	7 27 $P < 0.0001$	77 83 $P = 0.029^a$
Hiddemann et al., 2005 [22]	CHOP, 205R-CHOP, 223	18	9096	17 <sup>b</sup> 20 <sup>b</sup>	29 NR $P < 0.001$	90 95 $P = 0.016^c$
Herold et al., 2007 [23]	MCP, 96R-MCP, 105 26 (4 years 36%)	47 74	7592	25 <sup>b</sup>  50 <sup>b</sup>	NR (4 years 69%) $P < 0.0001$	87 $P = 0.0096^d$
Foussard et al., 2006 [24]	CHVP-IFN, 175R-CHVP-IFN, 183	42	7281	60  75	4667  (EFS) $P < 0.0001$	84  91 $P = 0.029$

Table 1 courtesy of M. Herold.

<sup>a</sup>Estimated 4-year OS.

<sup>b</sup>Patients who fulfilled CR criteria but had no evaluable negative BM biopsy defined as PR, not CRu.

<sup>c</sup>Estimated 2-year OS.

<sup>d</sup>'Estimated' 4-year OS.

Abbreviations: CR, complete remission; *f/u*, follow-up; NR, not reached; ORR, overall response rate; OS, overall survival; TTF, time-to-treatment failure.

to delineate the best approach in patients with FL from these trials. A risk-adapted procedure may be most adequate.

### relapsed disease and rituximab

The addition of rituximab to salvage chemotherapy improves the response rates and prolongs OS in relapsed and refractory follicular and mantle cell lymphoma. Chemotherapy may consist of standard CHOP in patients not previously treated with an anthracycline-containing regimen [25] or the more aggressive fludarabine–cyclophosphamide–mitoxantrone (FCM) regimen [26] in patients pretreated with CHOP. The ORR was increased by 15–20% in both studies if rituximab was added. Maintenance therapy with rituximab further improved the results. In the EORTC study reported by van Oers et al. [25], OS from second randomization was 85% with rituximab and 77% without rituximab at 3 years. The German Low Grade Lymphoma Study Group showed that OS at 3 years was 77% in patients with maintenance therapy and 57% after observation only [27].

### the role of radio-immunotherapy

The only randomized study comparing rituximab with [<sup>90</sup>Y]ibritumomab–tiuxetan in patients with relapsed or refractory indolent or transformed non-Hodgkin lymphoma (NHL) showed significantly higher ORR in patients treated with [<sup>90</sup>Y]ibritumomab–tiuxetan compared with patients given rituximab (80% versus 56%, *P* = 0.002). However, there was no significant difference in response duration [28]. Many more studies have shown that [<sup>90</sup>Y]ibritumomab–tiuxetan is active in patients with rituximab-refractory disease, that mild thrombocytopenia is not prohibitive for the use of [<sup>90</sup>Y]ibritumomab–tiuxetan and that collection of stem cells is feasible after [<sup>90</sup>Y]ibritumomab–tiuxetan administration. The most relevant question is whether [<sup>90</sup>Y]ibritumomab–tiuxetan or [<sup>131</sup>I]tositumomab is superior to re-treatment with rituximab chemotherapy in patients with relapsed/refractory FL who have been exposed to rituximab as part of first-line therapy. Unfortunately, no phase III data are available to answer this question.

Radio-immunotherapy has been used as single agent and as part of multi-agent therapy in first-line treatment of FL (Table 2).

Kaminski et al. [31] evaluated the efficacy of [<sup>131</sup>I]tositumomab therapy as a single agent in previously untreated advance stage FL. Seventy-six patients with stage III or IV FL received a standard dose of [<sup>131</sup>I]tositumomab. The ORR was 95%, with a CR rate of 74%. The 5-year PFS for all patients was 59% and the median PFS was 6.1 years, with a median follow-up of 5.1 years. The primary toxicity was moderate myelosuppression.

A phase II trial of CHOP chemotherapy followed by [<sup>131</sup>I]tositumomab was conducted by the Southwest Oncology Group (SWOG) in patients with previously untreated FL [34]. This trial enrolled 90 patients with bulky stage II, III or IV FL. The median age was 50 years, and 65% of the patients were in the intermediate to high FL International Prognostic Index (FLIPI) risk groups. Patients received six cycles of standard CHOP chemotherapy followed 4–8 weeks later by

**Table 2.** Radio-immunotherapy as first-line treatment of indolent lymphoma

Study	Combined regimen	No. of patients	Overall response (%)	Complete response (%)
[ <sup>90</sup> Y]Ibritumomab–tiuxetan				
DeMonaco et al. [29]	R-CHOP	8	87	100
Shiple et al. [30]	R-CHOP	42	87	67
[ <sup>131</sup> I]Tositumomab				
Kaminski et al. [31]	None	76	95	74
Leonard et al. [32]	Fludarabine	35	100	86
Link et al. [33]	CVP	30	100	80
Press et al. [34]	CHOP	90	91	69

[<sup>131</sup>I]tositumomab after restaging. The ORR was 91%, but was as high as 96% when six patients with insufficient data were excluded. The CR rate was 39% after six cycles of CHOP but improved to 69% after the [<sup>131</sup>I]tositumomab. The estimated 5-year OS and PFS were 87% and 67%, respectively, with a median follow-up time of 5.1 years. These numbers were superior to historical groups of patients treated with CHOP alone (5-year OS and PFS of 64% and 44%, respectively). Hematologic toxicities after [<sup>131</sup>I]tositumomab were generally milder than those after CHOP.

A number of trials have investigated either [<sup>131</sup>I]tositumomab or [<sup>90</sup>Y]ibritumomab–tiuxetan in conjunction with various other chemotherapeutic regimens, including fludarabine [32], CVP [33] or R-CHOP [29, 30], as first-line therapy for indolent NHL. All of these studies have shown excellent response rates with ORR ranging from 90% to 100% and CR rates of 60–90%. The treatments were well tolerated with no unpredicted toxicities and many patients achieved durable remissions of >5 years.

As in relapsed or refractory disease, there is no published study addressing the question of whether either [<sup>90</sup>Y]ibritumomab–tiuxetan or [<sup>131</sup>I]tositumomab given in conjunction with poly-chemotherapy results in better response and response duration than the combination of rituximab and the identical chemotherapy regimen as first-line therapy of FL. Given the fact that radio-immunotherapy is more cumbersome to administer and several other restrictions apply (e.g. no bone marrow involvement >25%) only such a study will convince the majority of oncologists to prefer radio-immunotherapy over immunotherapy with the naked antibody.

### aggressive T-cell lymphoma

The humanized anti-CD52 immunoglobulin G1 monoclonal antibody alemtuzumab (MabCampath) is increasingly being used to treat aggressive T-cell lymphoma. The single-agent activity has been modest (ORR 36% in a pilot study published by Enblad et al. [35]). Toxicity was severe and included cytomegalovirus (CMV) reactivation, pulmonary aspergillosis, pancytopenia and Epstein–Barr virus (EBV)-related hemophagocytosis. Currently, the combination of

alemtuzumab with the CHOP regimen is under investigation [36]. A prospective, randomized, phase III study conducted by the DSHNHL and the Nordic Lymphoma Group compares CHOP with A-CHOP.

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