Rituximab therapy for follicular lymphoma: a comprehensive review of its efficacy as primary treatment, treatment for relapsed disease, re-treatment and maintenance

YOSSI COHEN, PHILIPPE SOLAL-CÉLIGNY, AARON POLLIACK

Background. Advances in the treatment of follicular lymphoma (FL) have been achieved through the development of newer combination regimens, mostly based upon purine analogs and/ or monoclonal antibodies, as well as recent progress in the area of stem cell transplantation.

Information Sources. These advances have increased the need to obtain consensus regarding treatment priorities from the various options available, ranging from the traditional palliative approach through to the novel regimens available including stem cell transplantation.

State of the Art. The apparent synergism between chemotherapy and rituximab, which facilitates the achievement of complete clinical (CR) and molecular remission (MR), together with the possible feasibility of maintenance and re-treatment with rituximab have increased the interest in the use of this drug as primary treatment for FL. This review summarizes the available literature and deals with the role of rituximab in refractory/relapsed FL as well as in previously untreated FL patients. The improvement in remission rates and response duration associated with immunotherapy are contrasted with the potential risks, such as the development of rituximab resistance, as well as other less recognized complications related to altered humoral immunity.

Perspectives. Despite all the advances reported, treatment might still have to be individualized for patients with FL, until evidence of an important survival advantage for rituximab over chemotherapy is established. The possible role of autotransplantation for FL and the use of rituximab is also reviewed.

Key words: rituximab, follicular lymphoma, therapy, autulogous transplantation.

Haematologica 2003; 88:811-823
http://www.haematologica.org/2003_07/811.htm

From the Departments of Hematology, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan (YC), Centre Jean-Bernard Le Mans, France (PhS-C), Hadassah University Hospital (AP), Jerusalem, Israel.

Correspondence: Professor Aaron Polliack, MD, Head of Lymphoma-Leukemia Unit, Department of Hematology, Jerusalem, Hadassah University Hospital, Israel 91120. E-mail: rakefet1@012.net.il

Until a few years ago, the management of FL was basically palliative, usually starting with a *watchful waiting* approach,[1-3] and proceeding as deemed necessary with radiotherapy, oral alkylating agents and eventually combination chemotherapy. Despite the efficacy of regimens such as CVP (cyclophosphamide, vincristine, prednisone) and ProMACE-MOPP,[4-8] deferral of treatment appeared to have no influence on the survival of patients with FL. Furthermore, even classic anthracycline-containing regimens such as CHOP, did not produce any survival advantage over that provided by oral chemotherapy.[9-11] It is also still too early to predict the effect on survival of newer regimens based upon purine analogs[12-17] and/ or monoclonal antibodies.[18-24] However, recent progress in this area has renewed the interest in treatment with curative intent for FL, thereby complicating therapeutic decisions regarding the primary management of young patients with FL. In fact, the major dilemma today in previously untreated patients is whether to start novel treatments, which will enable uncontaminated stem cell grafts, minimally exposed to chemotherapy, to be harvested or whether to preserve these newer regimens for salvage, thereby reducing the risk of early resistance to these drugs. This review summarizes the relevant literature, deals with the role of rituximab as primary and second-line therapy for FL, relating to the efficacy of rituximab as maintenance therapy and retreatment. We also review the use and the role of rituximab in stem cell transplantation (SCT) for FL.

Rituximab therapy in chemoresistant relapsed follicular lymphoma

Rituximab alone

A series of phase II studies, a phase III trial comparing rituximab and ^{90}Y ibritumomab tiuxetan (zevalin), and the pivotal trial have assessed the efficacy and safety of rituximab in relapsed/ refractory indolent lymphoma.[18-28] Excluding the study by Piro *et al.*,[19] which used 8-weekly infusions of rituximab (375 mg/m^2), all other studies employed 4-weekly cycles at the same dose. In all series, most of the patients had advanced stage disease at the time of treatment and a small proportion had also received a prior autotransplant. Between 21% and 63% (mostly about 50%) achieved an objective response following treatment (Table 1), but only a minority (up to 24%) had a CR. Of the BCL-2$^+$ FL patients, about half converted to polymerase chain (PCR) negativity in the peripheral blood (PB) and/ or bone marrow (BM) samples, however the correlation between molecular remission status and clinical outcome was limited.[22,25]

Table 1. Clinical trials using rituximab alone in refractory/relapsed indolent lymphomas.

Study (reference, year)	*No. of pts. (evaluable)*	*Median age, yrs (range)*	*Disease*	*Stage III/IV (%)*	*RR (%)*	*CR (%)*	*TTP/ RD, median, months*	*MR*
Maloney[18] (1997)	37 (34)	58 (29-81)	Entire group FL= 86% SLL= 11% MCL=3%	76°	50 56 0 0	9 9 0 0	10.2/ 8.6	NA
Piro[19] (1999)	37 (35)	55 (35-74)	Entire group FL= 79% SLL= 19% E*=3%	68#	60 69 14	14	>19.4/ >13.4	PB: 9/18 (50%)
Nguyen[20] (1999)	48	57 (36-81)	Entire group FL= 46% S/CLL= 31% MCL=21% DLCL = 2%	92	21 27 6 20	0	NA/6	NA
Davis[21] (1999)	31 (28)	55 (33-79)	Entire group FL= 71% SLL=29%	68	43 55 0	4	8.1/5.9	NA
Foran[22] (2000)	70@	50 (35-77)	FL	NA	46	3	NA/ 11	PB and/or BM: 13/21 (62%)
Case[23] (2002)	38	65 (37-87)	FL	100	63	8	NA/ 4	NA
Feuring-Buske[24] (2000)	38 (30)	55 (26-75)	FL (grade I/II)	100	47	17	6.7/ 5.9	NA
Ghielmini[25] (2000)	120	57 (31-78)	FL= 65%	84	52	3	NA	PB: 15/29 (52%) BM: 5/23 (22%)
		65 (45-83)	MCL= 35%	90	22	0	NA	PB: 5/12 (42%) BM: 0/7
Walewski[26] (2001)	38 (34)	53 (29-75)	Entire group FL=63% LPL=16% SLL=11% MCL=8% MALT=3%	NA	59	24	16/ NA	NA
Witzig[27] (2002)	70	57 (36-78)	Entire group FL= 83% SLL= 11% Trans=5.7%	91	56 55 50 75	20	10.1/ 12.1	NA
McLaughlin[28] (1998)	166 (151)	58 (22-79)	Entire group FL= 78% SLL= 20% Other=2%	88.4	50 60 13	6	13/11.2	PB:26/45 (58%) BM: 9/16 (56%)

**Histologic group based on Working Formulation; Stage unknown in 5%°, 19%#; @22 of the patients were included in the report by Nguyen et a.l[20]; RR, response rate; CR, complete remission; TTP, time to progression; RD, response duration; MR, molecular remission; FL, follicular lymphoma; SLL, small lymphocytic lymphoma; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; DLCL, diffuse large B-cell lymphoma; LPL = lymphoplasmacytic lymphoma; MALT, mucosa-associated lymphoid tissue; Trans=transformed; PB, peripheral blood; BM, bone marrow; NA, not available.*

Despite the heterogeneity of the patients' characteristics and prior treatments among the different groups, the response rate in the pivotal trial, which included 166 pretreated patients with indolent lymphoma (< 10 cm lesion) was quite similar, approaching 50% (60% in FL), with 6% CR.[28] The presence of bulky disease (> 5 cm lesion) was associated in some of the studies with lower response rates,[19,24,28,69] but this observation was not supported by the study by Davis *et al.*,[21] which was designed for patients with bulky disease (> 10 cm lesion), and in which a 55% response rate was found among the FL subset. However, consensus does exist in relation to the observation that the response to rituximab is higher among patients with FL (27-69%) than in those with mantle cell lymphoma (MCL) (20-22%),[20,25] and chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) (0-50%).[18-21,27,28] Despite the

Table 2. Clinical trials using rituximab combined with chemotherapy in refractory/relapsed indolent lymphomas.

Study (reference) (year)	No of pts (evaluable)	Median age, years, (range)	Disease	Stage III/IV	Regimen	RR (%)	CR (%)	TTP/ RD, median, months	MR
Hiddemann *et al.*[29] (2002)	80	NA	FL= 54% MCL=34% Others=12%	NA	FCM×4	53 (68 in FL)	15	NA	NA
					FCM-R×4	89 (95 in FL)	36	NA	NA
Herold *et al.*[30] Hirt[112] (2002)	106	NA	FL=78%, MCL=22%	100%	MCP×8 or MCP-R×8	81°	40	NA	PB: 0/12* PB: 15/17 (88%)
Sacchi *et al.*[31] (2002)	48 (39)	62 (44-71)	FL	NA	FC-R×4	97	74	NA/13	BM: 15/18 (83%)
Weide *et al.*[32] (2002)	45	70 (36-82)	IL = 56% C/PLL= 36% HGL = 9%	100% for IL	BM (up to x 5) + R	96	42	26/NA	NA

*RR, response rate; CR, complete response; TTP, time to progression; RD, response duration; MR, molecular remission; NA, not available; FL, follicular lymphoma; MCL, mantle cell lymphoma; IL, indolent lymphoma; C/PLL, chronic lymphocytic/ prolymphocytic leukemia; HGL, high grade lymphoma; R, rituximab (375 mg/m²); FCM, fludarabine 25 mg/m² d 1-3, cyclophosphamide 200 mg/m2 d 1-3, mitoxantrone 8 mg/m²; FC, fludarabine 30 mg/m² d 1-3, cyclophosphamide 300mg/m² d 1-3; MCP, mitoxantrone 8 mg/m² d 3-4, chlorambucil 9 mg/m² d 3-7, prednisolone 25 mg/m² d 3-7 (R d 1); BM, bendamustine 80 mg/m², d 1-3, (80 mg/m², d 1-2 in CLL), mitoxantrone 10 mg/m², d 1, rituximab at weeks 2,3,4,5; *BCL-2; °No difference between the 2 arms.*

fact that in several cases the progression-free survival (PFS) following rituximab therapy exceeded that obtained after the preceding chemotherapy regimen given,[24] responses after monotherapy with rituximab were mostly partial and not durable, which is not too surprising in such heavily pretreated cases. There are currently few data regarding the long-term outcome following treatment with rituximab, however the median time to progression (TTP) was between 6.7 and >19.4 months (13 months in the pivotal trial), with a median response duration (RD) between 4 to >13.4 months (11.2 months in the pivotal trial). It is noteworthy that the clinical responses did not correlate with age, IPI, performance status, or serum lactate dehydrogenase/β-2 microglobulin levels, but showed an inverse relationship with the number of prior relapses.[22,28]

Rituximab in combination with chemotherapy

The established efficacy and low toxicity of rituximab as monotherapy soon led to studies employing rituximab in combination with chemotherapy.[19-28] Of the four clinical trials reported in pretreated FL (Table 2), two were comparative with one arm receiving chemotherapy alone and the other chemotherapy combined with rituximab. The study by Hiddemann *et al.*[29] enrolled 80 patients (FL, 54%; MCL, 34%, others 12%) who received 4 cycles of either FCM (fludarabine, cyclophosphamide, mitoxantrone) or FCM + rituximab. Results showed an improvement in the response rate from 53% (68% in FL) after FCM to 89% (95% in FL) following therapy with rituximab, and in the CR rate from 15% to 36%, respectively. In contrast to the results of this study, there was no advantage in outcome after using the combination of MCP (mitoxantrone, chlorambucil, prednisolone) + rituximab as opposed to MCP alone, in the study reported by Herold *et al.*[30] The overall response rate was 81% with a CR rate of 40%, without any statistical difference between the two arms. The contrast in the results of the above two studies regarding the additive contribution of rituximab to the clinical response beyond that obtained by the chemotherapy itself can be attributed to the difference in intensity of the chemotherapeutic schedule used, which resulted in a similar overall response and especially complete remission rates following 8-cycles of MCP alone (81% and 40%, respectively), as in the two studies employing 4-6 cycles of combination chemoimmunotherapy (89-96% and 36-42%, respectively).[29,32] Other differences, such as the median number of previous chemotherapy regimens before registration into the trials, might also play a role in this regard.

The other two studies consisted of a chemoimmunotherapy arm alone. In the study by Sacchi *et al.*,[31] 48 pretreated FL patients received 4 cycles of FC (fludarabine, cyclophosphamide) + rituximab and the response rate in the intent-to-treat analysis was 97%, with 74% CR. Overall, 8 patients relapsed (21%), and 3 died (one due to severe neutropenia during chemotherapy and two due to lymphoma progression). The study by Weide *et al.*[32] included 45 patients with either advanced stage indolent lymphoma (56%), CLL/PLL (36%) or high-grade lymphoma (9%), receiving rituximab together with bendamustine and mitoxantrone. The overall response rate after chemoimmunotherapy approached 96% and the CR rate 42%. When compared to studies using rituximab alone,[18-28] combining rituximab with chemotherapy in pretreated patients with FL was

Table 3. Clinical trials using rituximab combined with immunoadjuvants in refractory/relapsed indolent lymphomas.

Study[ref] (year)	*No. (evaluable)*	*Age, median, (years)*	*Disease*	*Stage III/IV*	*Regimen*	*RR %*	*CR %*	*TTP/ RD median, months*
Davis *et al.*[36] (2000)	38	53 (31-80)	FL= 89% SLL= 11%	73%*	[1]IFN-α-2a + R×4	45	11	25.2/22.3
Bron *et al.*[37] (2002)	70	NA	Indolent lymphomas	NA	R×4→[2]IFN-α-2a	49 41	10 19	>18/20
Sacchi *et al.*[38] (2001)	64	54 (29-74)	FL= 89% SLL=11%	84%	R×4 + [3]IFN-α-2a	70	33	NA/ 19
Friedberg *et al.*[40] (2002)	20	50 (27-73)	FL	95%	[4]IL-2 + R×4	55	5	> 13/ NA
Ansell *et al.*[41] (2002)	43	54 (34-84)		FL=47% DLCL=26% MCL=14% SLL=9% LPL=4%	R x 4 + [5]IL-12	69	26	NA/ >8 26
McLaughlin *et al.*[42] (2001)	13 (12)	51 (35-77)	FL=92% Other=8%	NA	R x 4 + [6]GM-CSF	83	42	>9/ NA
Rossi *et al.*[43] (2001)	39 (35)	NA	FL= 74% MCL = 10% Others =16%	80%	R×4 (q 3 w) + [7]GM-CSF	60	40	NA

*RR: response rate; CR: complete response; TTP: time to progression; RD: response duration; FL: follicular lymphoma; SLL: small lymphocytic lymphoma; DLCL: diffuse large cell lymphoma; MCL: mantle cell lymphoma; LPL: lymphoplasmacytic lymphoma; R: rituximab (375 mg/m²); IFN: interferon; [1]IFN 2.5 or 5 MIU, 3 ×wk for 12 wks; [2]IFN 3 MIU/m² at TIW for 6 m, R at weeks 5,6,7,8; [3]IFN 1.5 → 6 MIU/d for 5 wks; [4]IL-2 1·2 MIU/m²/d for 56 d; [5]IL-12 30 → 500 ng/kg ×2/ wks up to 24 wks; [6]GM-CSF 250 μg 3 ×/w x 8 wks; [7]GM-CSF 5 μg/kg/, d 1-8; *5% stage unknown.*

associated with improved overall response and CR rates. However, there are still very limited and inconsistent data on long-term response parameters, with the median response duration of 13 months in the study by Sacchi *et al.* being similar to that reported in the pivotal trial, but with a TTP of 26 months in the study by Weide *et al.* compared to 13 months in the pivotal trial.

Therapy with rituximab was strongly associated with molecular remission (MR), and in the study by Hirt *et al.*,[112] MR was evident in the peripheral blood samples of 15/17 (88%) FL patients treated by MCP (mitoxantrone, chlorambucil, prednisolone) + rituximab compared with 0/12 patients treated by MCP alone. Furthermore, the combination of rituximab with fludarabine-based regimens yielded MR in the marrow of 15 of 18 (83%) treated patients examined by molecular markers.[31] Additional second-line chemoimunotherapy combinations currently under clinical investigation include CHASER (cyclophosphamide, Ara-C, etoposide, dexamethasone, rituximab),[33] R-DHAP[34] and R-ESHAP.[35]

Rituximab in combination with immunoadjuvants

A number of immunoadjuvants have been studied in combination with rituximab in refractory/relapsed indolent lymphomas (Table 3). Interferon (IFN)-α-2a enhances the surface expression of CD20 antigen, and thereby can augment antibody-dependent cell-mediated cytotoxicity (ADCC) induced by rituximab. Two of three studies, combining IFN-α-2a with rituximab resulted in an overall response of 41-45% with 11-19% CR,[36,37] which are in fact comparable to results of rituximab monotherapy.[18-28] However, the third study by Sacchi *et al.*[38] yielded much higher overall responses and CR rates of 70% and 33% respectively. Furthermore, even in the study by Bron *et al.*,[37] there was an increase in the CR from 10% after rituximab to 19% after IFN-α-2a, which is consistent with the preliminary results obtained from the comparative study reported by Kimby,[39] indicating that IFN-α-2a appears to improve the response obtained with rituximab alone. However, the improved CR rate in the study by Bron *et al.* could also have resulted from a delayed response to rituximab alone. Thus, it is still difficult to determine the true effect of IFN-α-2a on response rates of patients with indolent lymphomas, and whether the differences in outcome reported in these studies were influenced by differences in dosage and treatment schedules (Table 3), or even by variations in the definitions and inclusion criteria used. On the other hand, the median response duration in all these three studies is about the same (20 months), and when compared to the median response duration of 13 months in the pivotal study, it appears that IFN-α-2a may have a positive role in prolonging the response to rituximab.

Interleukin 2 (IL-2) is also an enhancer of ADCC, and was recently examined in combination with rituximab in refractory/ relapsed FL. Preliminary results

Table 4. Clinical trials using rituximab alone in previously untreated follicular lymphoma.

Study[ref] (years)	No.	Median age, yrs (range)	Disease	Stage III/IV	Regimen	RR (%)	CR (%)	PFS at 3-yrs	TTP/ PFS, median	MR
Hainsworth *et al.*[48] (2002)	60	65 (27-89)	FL=61% SLL=39%	76%	R×4→ Rq6 m×4	47 73°	7 37°	49%	NA/34	NA
Solal-Céligny *et al.*[49] (2002)	49	52 (32-75)	FL (low tumor burden)	94%	R×4	73 80*	26 41*	32%	18.4/ NA	PB: 17/32 (53%) BM: 7/29 (24%)
Witzig *et al*[50] (2002)	37	59 (29-83)	FL (grade I)	100%	R×4	61	25	NA	20/ NA	NA

*RR: response rate; CR: complete response; PFS: progression-free survival; TTP: time to progression; MR: molecular remission; FL: follicular lymphoma; SLL: small lymphocytic lymphoma; R: rituximab (375 mg/m^2); NA: not available; PB: peripheral blood; BM: bone marrow; *maintenance R courses (4 weekly infusions at 375 mg/m^2) at 6-month intervals for a maximum of 4 courses or until progression; Best response °after one or more maintenance courses, *during the year following treatment.*

show a 55% overall response with 5% CR.[40] IL-12 facilitates cytolytic T- and NK-cell activities and stimulates the secretion of IFN-γ by these cells. In a phase I study of 43 adults with B-cell lymphoma, combination immunotherapy with IL-12 and rituximab resulted in a 69% overall response and 26% CR.[41] The combination of GM-CSF and rituximab has also been examined in two recent studies of patients with refractory/ relapsed indolent lymphoma, yielding 60-83% overall response rates with impressive CR rates of 40-42%.[42,43] Other immunoadjuvants and rituximab combinations under current assessment include Favid, a tumor-specific B-cell immunoglobulin idiotype protein complexed with KLH, utilized for induction of active immunity in indolent lymphomas,[44] as well as thalidomide and its analog revimid.[45]

Finally, combining rituximab with a second anti-lymphoma monoclonal antibody, such as apolizumab (Hu1D10)[46] (a humanized IgG1 antibody directed against the HLA-DRa chain CD10 antigen, expressed on the majority of B-cell lymphomas) or the radioimmunoantibody yttrium-90 ibritumomab tiuxetan (zevalin), also seems to be a novel and exciting approach, with the latter combination being predicted to yield both earlier reduction in the tumor size due to the effect of zevalin, as well as a longer response duration because of the effect of rituximab.[47]

Rituximab as primary treatment for follicular lymphoma

Single agent therapy with rituximab

Three recent clinical trials have addressed the efficacy of rituximab in previously untreated indolent lymphomas, mostly in advanced disease (Table 4).[48–50] In two of the studies[49,50] all patients had FL, whereas in the study by Hainsworth *et al.* SLL patients were also included (39%). In addition, it should be stressed that the study by Solal-Celigny *et al.*[49] was designed for patients with a low tumor-burden, while that of Witzig *et al.*[50] was for patients with grade I FL. Finally, the study by Hainsworth *et al.*[48] was exceptional in that the patients continued up to 4 maintenance courses of rituximab at 6-month intervals after initial induction with rituximab. Response rates in these studies ranged between 61% and 80% and the CR rates between 25% and 41%. Compared with the results in pretreated groups (Table 1), those of the studies reported in previously untreated FL appear to be better, and are consistent with the reported inverse relationship between the number of prior relapses and the response to rituximab monotherapy.[22,28]

Rituximab in combination with chemotherapy

Exploiting the observation that the toxicity profiles of chemotherapy and rituximab do not overlap, and that rituximab is able to sensitize lymphoma cells to chemotherapy,[52] a variety of chemoimmunotherapy combinations have been studied for their potential role in primary treatment of FL, mostly at an advanced stage (Table 5). In 4 of the studies[53–56] Rituximab was combined with CHOP; in the study by Czuczman *et al.*[53] this combination was employed concurrently, whereas in the other 3 studies rituximab was used sequentially as consolidation (4-weekly infusions) after completing all the cycles of CHOP. After the concurrent CHOP + rituximab combination, there was 100% response and 63% CR, whereas at the end of the consolidation schedules with rituximab, between 72 and 100% of the patients in each study group were seen to have responded, with 54-87.5% CR. The latter results also reflect the 19-39% improvement in CR rates following immunotherapy compared to the 35% to 58.5% CR rates following CHOP chemotherapy and before giving rituximab.[54–56] When comparing the two treatment schedules, it appears that both the concurrent CHOP + rituximab regimen as well as the tandem of CHOP regimens followed by sequential rituximab yielded comparable overall responses and CR rates. This observation is also supported by limited data at

Table 5. Clinical trials using rituximab combined with chemotherapy in previously untreated follicular/low grade lymphoma.

Study[ref] (year)	*No. (evaluable)*	*Age, median, years (range)*	*Disease*	*Stage III/IV (%)*	*Regimen*	*RR (%)*	*CR (%)*	*TTP/ RD, (median, months)*	*PFS/DFS (median, months)*	*MR*
Czuczman *et al.*[53] (2002)	#40 (35)	53 (40-77)	FL=73% SLL=27%	83	CHOP- R x 6	100	63	>52.1 >50.4	75% (29)/NA	7/8 (87) (PB+ BM)
Maloney[54] (2001)	85 (84)	53 (22-76)	FL	91	CHOP×6 → *R×4	72	35 54	NA	76% (24) ### /NA	NA
Jaeger *et al.*[55] (2002)	41	53.5 (33-75)	FL	87	CHOP x 3-6 → *R×4	100	58.58 87.5	>24.3/ NA	76% (24.3) /NA	5/9 (56) (PB+ BM)
Czuczman *et al.*[57] (2001)	40## (34)	55.5 (40-77)	FL=73% SLL=27%	100	[1]F- R	90	82.5	NA/ >15	NA	NA
Vitolo *et al.*[58] (2002)	59 (36)	66 (60-78)	FL	87	[2]FMD×4 → R×4	95	48 90	NA	NA	6/18 (33) 15/18 (83)
Zinzani *et al.*[56] (2002)	93	NA (15-70)	FL	NA	[3]FM×6 → R×4 **R×4	94	68 87	NA	NA	BM: (34) BM: (59)
					CHOP ×6→ **R x 4	93	37 76			BM: (20) BM: (40)
Cohen *et al.*[59] (2002)	33	48 (24-59)	FL	91	[4]FC×4-6→ *R×4	87.9	84.8	NA	NA/63.4 (24)	19/25 (76)
Gregory[60] (2002)	41 (31)	NA	FL=59% SLL=27% MCL=7% Others=9%	88	[5]FM×4-6→*R×4	97	45	NA	NA	NA

*Treatment naive: #67.5%, ##60%; ###Two-year PFS rate; RR: response rate; CR: complete response; TTP: time to progression; RD: response duration; PFS: progression-free survival; DFS: disease-free survival; MR: molecular remission; FL: follicular lymphoma; SLL: small lymphocytic lymphoma; MCL: mantle cell lymphoma; PB: peripheral blood; BM: bone marrow; NA: not available; R: rituximab (375 mg/m^2); [1]F, fludarabine 25 mg/m^2 d 1-5; [2]FMD, fludarabine 25 mg/m^2 d 1-3, mitoxantrone 10 mg/m^2 d 1, dexamethasone 20 mg/m^2 d 1-3, additional 2 cycles of FMD and R were given to PR pts; [3]FM, fludarabine 25 mg/m^2 d 1-3, mitoxantrone 10 mg/m^2 d 1; [4]FC, fludarabine 25 mg/m^2 d 1-3, cyclophosphamide 250 mg/m^2 d 1-3; [5]FM, fludarabine 25 mg/m^2 d 1-3, mitoxantrone 12 mg/m^2 d 1; Eligibility to R included *PR/ CR after chemotherapy and **PCR+ in BM/ PB.*

24-29 months post-treatment showing similar PFS rates of about 75-76% following either schedule (Table 5).[53-55]

The second chemotherapeutic regimen studied in combination with rituximab was based on fludarabine, either alone[57] or with mitoxantrone,[56,58,60] cyclophosphamide[59] or steroids. As with CHOP, rituximab was given either concurrently[57] or following combination chemotherapy.[56,58-60] With either schedule response rates were impressive, approaching 88% to 97% with 82.5-90% CR, except for the study by Gregory *et al.*, in which only 45% of patients achieved a CR, possibly due to inclusion of 41% non-FL cases.[60] In the two studies for which data were available, there was improvement in the CR rate from 68% and 48% after chemotherapy to 87% and 90%, respectively, after the administration of rituximab.[56,58]

As with CHOP+rituximab combinations, there was no major difference in results between the concurrent fludarabine-rituximab regimen versus most studies using rituximab as consolidation, but it must be remembered that the wide range in time (even months) for the maximal effect of rituximab, and the exclusion of chemoresistant cases from subsequent consolidation,[56,59] preclude fair comparison between the two treatment schedules.

From these studies it also appears that the rituximab + fludarabine combination regimens tend to yield somewhat better CR rates than rituximab + CHOP (Table 5), and this tendency is indeed supported by the single two arm study reported by Zinzani *et al.*,[56] showing 87% CR for the fludarabine + rituximab arm versus 76% for the CHOP + rituximab arm, but it must be stressed that no long-term data is currently available.[56]

Finally, in all relevant studies rituximab showed its impressive ability to induce MR, and to improve the MR rate achieved by chemotherapy;[56] nevertheless, neither the achievement of MR nor CR guaranteed prolonged complete remission. This is reflected by the results of a study of Cohen *et al.*,[59] in which 8/28 CR and 5/19 MR patients eventually relapsed; this issue is further discussed below.[79-90] Other chemotherapeutic regimens now under clinical assessment in conjunction with rituximab include CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone),[61] cyclophosphamide/pentostatin,[62] and chlorambucil.[63]

Table 6. Clinical trials using rituximab as re-treatment in follicular lymphoma.

Study[ref] (year)	No. (evaluable)	Disease	Retreatment regimen	RR (%)	CR (%)	[1]PFS or [2]TTP/RD months (after the first R course)
Igarashi *et al.*[64] (2001)	13	IL	R×4	38	0	15.1 (8.2)/ NA
Davis *et al.*[65] (2000)	58 (57)	FL=95% SLL=5%	R×4	40	11	[2]17.8# (12.4)/ 16.3* (9.8)
Coiffier *et al.*[66] (2002)	59	B-NHL	R×4 +chemotherapy	93	42	[2]20 (12)/ NA

*RR: response rate; CR: complete remission; PFS: progression-free survival; TTP: time to progression; RD: response duration; IL: indolent lymphoma; FL: follicular lymphoma; SLL: small lymphocytic lymphoma; NHL: non-Hodgkin's lymphoma; R: rituximab (375 mg/m²); NA, not available; *Kaplan-Meier estimates.*

The feasibility of rituximab as re-treatment

Considering the prolonged clinical evolution of FL patients, who frequently require multiple courses of treatment, the incidence of rituximab resistance after repeated courses has major implications for treatment planning. Recently, this issue was addressed specifically in three clinical trials (Table 6). In a Japanese study of 13 patients with relapsed indolent lymphoma, 38% responded to a second course of rituximab, but none achieved a CR.[64] Davis *et al.*,[64] studied 58 FL patients who had received at least two prior therapies and at least one earlier course of rituximab, with a median interval of 14.5 months between rituximab courses. The overall response rate in 57 assessable patients was 40% with 11% CR. Finally, Coiffier *et al.*[66] followed a group of 59 NHL patients who were re-treated with rituximab either alone or with chemotherapy. Results showed 93% response to the second course of rituximab, with 42% CR. In addition, 12 of the 20 patients who progressed after the second rituximab treatment received a third cycle of the drug, and all responded again with a median TTP of 13 months. Interestingly, in both the series of Davis *et al.* and the French series the median TTP after rituximab retreatment was longer than that seen after the first course of rituximab (Table 6), although the differences were not statistically significant. Thus these and other reports[67] suggest that retreatment with rituximab either alone or with chemotherapy is indeed feasible and can induce longer response durations than those obtained following the initial use of rituximab. It must, however, be remembered that the results of these studies are biased by the inclusion of a selected population of patients (e.g. in the French study only 50% of the relapsed patients who had had prior rituximab therapy received rituximab re-treatment), Therefore, the results of the above three studies by no means indicate an equal efficacy of rituximab given in repeated use as opposed to standard regimens.

Maintenance rituximab therapy

By virtue of its low toxicity profile and considering the limited data suggesting that longer response durations can be achieved by the use of more cycles of rituximab than with the standard 4-cycle course,[19,48] the question of whether rituximab maintenance has a clinical benefit is of considerable importance. In a study by *the Swiss Group for Clinical Cancer Research* (SAKK), 151 FL patients with either newly diagnosed or resistant/ relapsed FL in remission or those with stable disease, were randomized between observation alone versus 4 maintenance infusions of rituximab at an 8-week interval following standard rituximab induction (Table 7).[68] The groups were equally balanced in age, PS (0-1: 97%), stage III-IV, bone marrow involvement (52%), elevated LDH (30%) and prior radiotherapy (18%) or chemotherapy (66%). With a median follow-up of 35 months, the median event-free survival (EFS) was 12 months for the observation arm vs 23 months for the maintenance arm (HR = 0.57). The difference in EFS was even more pronounced in the chemonaive subgroups (19 vs 36 months, respectively). Among all responders to rituximab, remissions at 12 months were sustained in 56% of patients in the observation arm vs 80% in the maintenance arm, with median response durations of 17 vs 36 months, respectively. Thus, maintenance rituximab therapy was associated with a 43% risk-reduction of disease progression/relapse in the entire group, and a 55% reduction among rituximab responders.

An alternative maintenance regimen requires re-administration of rituximab in order to maintain serum levels >25 μg/mL. In a group of 31 patients with relapsed B-cell lymphoma (18 with FL), receiving standard rituximab induction followed by maintenance rituximab infusions for 12 months, 57% responded to induction and 76% remained progression-free at a median follow-up of 12.5 months. Preliminary data showed a decrease in the median rituximab plasma levels from 407 μg/mL after the 4th infusion to 17 μg/mL at 6 months. Median times for the first and second maintenance doses were 5 and 9 months, respectively, and the number of maintenance cycles was between 1 and 3. In practice, a single maintenance infusion of rituximab provided adequate serum rituximab levels for 12 months in most patients.[69]

It is also worth mentioning the study by Hainsworth *et al.*[48] in previously untreated FL patients. The regimen used consisted of rituximab induction supplemented by identical dose and schedule maintenance cycles at 6-month intervals for a maximum of four cycles or until progression (Table 4). At 3 years, 49% of patients remained progression-free, compared to 32% in another group of FL patients treated by standard courses of rituximab but without

Table 7. Clinical trials using maintenance rituximab therapy for follicular lymphoma.

Study[ref] (year)	No. (evaluable)	Age, median, years	Disease	Stage III/IV	RR after R induction	%CR at 1/12/ >12 months	Maintenance method	%EFS[1] or PFS[2] (median follow-up, months)	EFS/ RD, median (months)
Ghielmini *et al.*[68]	185 (151)	57	FL	85	54 (%)#	10/23/29*	Observation	[1]56% (12)	12/17
							R q 8 wks (×4)	[1]80% (12)	23/36
Gordan *et al.*[69]	31 (28)	59	IL=75%	84	62%	NA	R (1-year) to	[2]76% (12.5)	NA
			IGL=25%		43%	NA	serum levels >25 μg/mL°	NA	NA

*RR: response rate; R: rituximab; CR: complete response; EFS: event-free survival; PFS: progression-free survival; RD: response duration; FL: follicular lymphoma; IL: indolent lymphoma (including 18/31 FL pts); IGL: intermediate grade lymphoma; NA: not available; RR: #46% for pretreated and 67% for chemonaive; *no difference between observation and maintenance arms; °1-3 infusions.*

maintenance rituximab cycles.[49] These results support the positive role and effect of maintenance rituximab infusions on response durations. However, the real long-term clinical benefits of this approach can only be assessed in comparative studies.

Disadvantages of using rituximab as primary therapy for follicular lymphoma

In addition to typical side effects, such as drug allergy and a degree of myelsuppression associated with the use of rituximab, concern also exists about some less well defined complications related to its effect on humoral immunity, as manifested mostly by increased susceptibility to infections,[70] and clonal selection of CD20 negative cells.[71-72] Regarding infections, it is worth recording the results of a clinical study of 17 FL patients receiving rituximab + fludarabine and cyclophosphamide, which was terminated due to excessive toxicity and infectious complications.[73]

The mechanism of $CD20^-$ selection involves down-regulation of CD20 protein in parallel to down-modulation of CD20 mRNA.[74] Clinically, by analysis of lymphatic tissue before and after rituximab therapy, there was complete or major loss of CD20 expression on persistent/relapsed lymphoma cells.[75] Such manifestations are occasionally seen with relapse at unusual sites, including muscle and subcutaneous nodules.[76] Furthermore, absence of CD20 expression on both B-CLL cells and the large cell component in Richter's transformation has also been described following rituximab therapy,[77] and in these cases it was evident, from sequencing of the Ig heavy chain, that the relapsed tumors originated from the $CD20^-$ CLL clones. These findings may imply the existence of causal relationships between the immunotherapy and clonal evolution/ large-cell transformation.[78] If this is indeed the case, one could speculate that the risk of clonal selection of CD20 negative cells might be reduced by employing initial debulking of the main tumor mass using chemotherapy alone, thereby favoring the method of consolidation rituximab over concurrent use of rituximab + chemotherapy.

Autotransplant for follicular lymphoma in the era of rituximab

The advances in the methodology of SCT with the development of improved *in vivo/in vitro purging* techniques have increased the interest in SCT for FL. Although persistence of $BCL\text{-}2^+$ cells after radio-or chemotherapy does not always predict clinical relapse,[79-83] post-transplant recurrence of Bcl-2/IgH positive cells, which occasionally involve different breakpoints, usually heralds clinical relapse.[84-89] Thus, the achievement of MR seems to be a major goal in the setting of SCT. Currently, the most sensitive method for monitoring molecular markers of FL such as t(14; 18) and IgH gene rearrangement is by real-time PCR, which shows positive results in about 1/3 of the cases of FL, but also in about 2% of the normal population.[90]

Although *ex vivo* purging can clear residual neoplastic cells from the stem cell harvests, this procedure is expensive, cumbersome and time-consuming.[91,92] The GITMO developed an *in vivo* purging method using sequential high-dose chemotherapy consisting of 2 induction cycles (doxorubicin, vincristine, prednisone, supplemented by DHAP×2 if CR is not achieved) followed by stem cell mobilization (etoposide, high-dose methotrexate, cyclophosphamide) and finally SCT (mitoxantrone/melphalan 180 mg/m^2).[93] This regimen, used in a group of 42 previously untreated patients with advanced stage FL, resulted in 48% MR, accompanied by sustained CR in 90% of patients with PCR-negative harvests. The projected overall survival and DFS for the PCR^- vs PCR^+ groups at 4 years were 84% and 67%, respectively; however, at publication of the report, 4 individuals had developed myelodysplasia, thus raising some doubts regarding the future feasibility of this procedure. Rituximab is effective and safe for *in vivo* purging methods,[94-110] but the ability to achieve MR depends on the type of regimen used, approaching 50% with the CHOP + rituximab combination, 66% with FM + rituximab, and 100% following high-dose therapy (HDT) + rituximab in previously untreated FL patients (63% in pretreated patients).[94]

Table 8. Summary of studies employing HDT and PBSCT for follicular lymphoma.

Study[ref] (year)	Disease (evaluable patients)	Age, median, (range)	Induction regimen	HDT regimen	Consolidation post HDT	CR (months)	MR (%)	Relapsed (median follow up)	Died
Ladetto *et al.*[104] (2002)	FL (45)	NA	R-HDS (n=21) R-CHOP (n=24)	R+ Mitox + Melph	–	75% of both arms (NA)	NA	NA	0 1
Brugger *et al.*[105] (2002)	FL (20)** MCL (10)	49 (31-60)	VACOP-B or CHOP → VIP-E or DexaBEAM	TBI (6×2 Gy) + cyclophosphamide (CD34+ selection)	R ×4	57% (6) 88% (12)	27/27	1/30 (24 m)	1
Buckstein *et al.*[106] (2002)	FL (49)***	44 (NA)	CHOP or DHAP CHOP or DHAP→Rx1 CHOP or DHAP + Rx3	CBV (n=14) CBV (n=23) CBV (n=12)	IFN-α-2a (24 m)# R×4 (+2, +6 m) R×6 + INF-α-2a (24 m)#	–##	10/12*	10/14 (51.6 m) 7/23 (34.8 m) 1/12 (4.8 m)	4

*HDT: high-dose therapy; CR: complete remission; MR: molecular remission; FL: follicular lymphoma; MCL: mantle cell lymphoma; NA: not available; R: rituximab; R-HDS: high dose sequential therapy: in vivo purging phase (cyclophosphamide 7 g/m² and cytarabine 1.5-2 g/m² every 12 hours for 6 consecutive days) → myeloablative phase (melphalan and mitoxantrone + melphalan), with reinfusion 1, 2×10⁶ CD34⁺ cells/kg, irrespective of PCR status; and reinfusions 2 and 3, 5 × 10⁶ and at least 8× 10⁶ CD34⁺ cells/kg, respectively, only if PCR negative; Mitox, mitoxantrone; Melph, melphalan; #IFN: 3 MU/m² tiw; ##Patients had to achieve > 75% reduction in tumor bulk to be eligible for transplant; **FL patients were newly diagnosed, MCL either newly diagnosed or relapsed; ***Relapsed/ refractory; *Sustained MR at follow-up of 18-48 months of all pts receiving R (MR was achieved at some point in most transplants).*

The role of rituximab in SCT was studied in three recent clinical trials reported in an abstract form. The GITMO[104] initiated a comparative study in patients with FL, with one arm receiving rituximab combined with sequential high dose therapy (R-HDS) (Table 8), and the second arm CHOP supplemented by rituximab. Preliminary results show an overall response rate of 79% with 75% CR for 45 evaluable patients from both arms.

The other two studies also used immunotherapy as post-transplant consolidation. In a German multicenter phase II study[105] including 30 newly diagnosed FL patients and newly diagnosed/ relapsed MCL patients, initial chemotherapy was started with VACOP-B or CHOP, followed by VIP-E or DexaBEAM. The HDT regimen included total body irradiation and cyclophosphamide, followed by CD34⁺ PBSCT. Rituximab (4-weekly, 375 mg/m²) was given at a median of 63 (38-108) days post-transplant. CR rates developed over time, being 57% at 6 months and 88% at 12 months. With a median follow-up of 24 months, 29 of the 30 evaluable patients remained in clinical CR. In addition, prior to HDT, 22% of the patients' PB and/or BM samples were PCR-negative. These numbers increased to 53% PCR negativity after HDT, 72% at 4 weeks after rituximab, and 100% at 6 months post-transplantation.

The Canadian study[106] enrolled 49 patients with refractory/ relapsed FL who responded to salvage chemotherapy (DHAP or CHOP × 4-5 cycles) into one of 3 post-transplant consolidation regimens: (I) IFN-α for 2 years; (II) rituximab (375 mg/m²) × 1 preceding the stem cell collection and then 4-weekly rituximab at 2 and 6 months post-transplant; (III) rituximab × 3 weekly combined with CHOP or DHAP prior to stem cell collection followed by rituximab × 6 weekly commencing 3-4 months post-transplant primed with IFN-α (3 MU/m² tiw) and continued for 2 years. With a median follow-up of 3 years (4.3 yrs IFN, 2.9 yrs rituximab and 0.4 yrs rituximab + IFN), 4 patients had died and 18 had relapsed (10/14 IFN, 7/23 rituximab and 1/12 rituximab + IFN) at median durations of 2.75, 1.8 and 0.4 years post-transplant, respectively. Interestingly, rituximab did not eliminate the molecular disease in most (23/29) PCR positive grafts, however MR was achieved at a later stage in most patients. MR was sustained in 10 of the 12 patients receiving rituximab (18-48 months), whereas recurrence of positive molecular markers heralded clinical relapse in 6/10 patients. Median relapse-free survival was 3.3 years for the IFN cohort and was not reached until publication in the rituximab or rituximab + IFN cohorts.

In general, rituximab appears to be well tolerated in the setting of ASCT and does not affect the recovery and function of stem cells,[107-109] or the levels of immunoglobulins.[110] In a retrospective analysis of 237 transplants for non-Hodgkin's lymphoma, a delay in engraftment was seen in patients who had had prior rituximab therapy compared to among the matched group who had not received the antibody. However, no difference in the incidence of post-transplant infection, duration of hospitalization, and 100-day mortality rate was apparent.

Conclusions

Despite the advances in the management of indolent lymphomas, the 5-year survival over the past two decades has remained the same (62-67%), and survival curves for these decades can be superimposed.[111] Currently, it is still too early to predict the influence on the life expectancy of novel therapies such as purine analogs and monoclonal antibodies,

although the improvement in response rates and in the quality of response are now well established. In pretreated FL, monotherapy with rituximab yields a 50% response rate but less than 10% CR, and chemotherapy must be added if CR remains one of the goals of therapy. In previously untreated FL, immunotherapy is more effective and induces CR in more than 40% of cases, and even higher CR rates are obtained when rituximab is combined with chemotherapy.

The influence of bulk *per se* on the efficacy of rituximab therapy remains controversial.[19-24,28,68] In fact this issue has not been specifically addressed until now, apart from in the study by Davis *et al.*,[21] which showed response rates of the same order as in other studies of pretreated FL patients. However, even in this study the CR rate only approached 4% (as in non-bulky FL), thereby still leaving the option of rituximab monotherapy in bulky FL as questionable. This obviously excludes the group of patients who are unable to tolerate chemotherapy.[51]

Finally, the risk of $CD20^-$ clonal selection and appearance of rituximab resistance must always be considered when planning primary treatment for FL patients, despite the established efficacy of rituximab retreatment in a proportion of patients.

In conclusion, there is still no standard approach for primary treatment of FL in the era of rituximab and purine analogs, and each of the following: watchful waiting, chemotherapy, immunotherapy or a combination of any of the above remains feasible. In our opinion, it seems logical to start rituximab in patients who are unable to tolerate chemotherapy, especially those with a low tumor burden. In addition, rituximab is appropriate treatment for young patients eligible for stem cell collection,[104-108] despite the fact that *in vivo* purging can essentially be reserved for the post-transplant period. In all other conditions, treatment must be individualized until long-term outcome results of ongoing studies and trials become available. The role of maintenance rituximab therapy is not established as yet but the encouraging preliminary results obtained recently[48,68-69] may eventually lead to changes in the current treatment schedules not utilizing rituximab maintenance.

References

1. Horning S, Rosenberg S. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 1984; 311:1471–5.
2. Horning S. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol 1993;20:75–88.
3. Brice P, Bastion Y, Lepage E, Brousse N, Haioun C, Moreau P, et al. Comparison in low tumor burden follicular lymphomas between an initial no treatment policy, prednimustine or interferon α: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. J Clin Oncol 1997;15:1110-7.
4. Hoppe RT, Kushlan P, Kaplan HS, Rosenberg SA, Brown BW. The treatment of advanced stage favorable histology non-Hodgkin's lymphoma: a preliminary report of a randomized trial comparing single agent chemotherapy, combination chemotherapy, and whole body irradiation. Blood 1981;58:592-8.
5. Lucas JB, Tibsharani R, Brophy N, Horning SJ. Follicular lymphoma in young patients: prognostic and survival data from the Stanford series. Blood 1999;94:2307a[abstract].
6. Longo DL, Young RC, Hubbard SM, Wesley M, Fisher RI, Jaffe E, et al. Prolonged remission in patients with nodular mixed lymphoma. Ann Int Med 1984;100:651-6.
7. Glick JH, Barnes JM, Ezdinli EZ, Berard CW, Orlow EL, Bennett JM, et al. Nodular mixed lymphoma: results of a randomized trial failing to confirm prolonged disease-free survival with COPP chemotherapy. Blood 1981;58:920-5.
8. Young RC, Longo DL, Glatstein E. The treatment of indolent lymphomas: watchful waiting vs. aggressive combined modality treatment. Semin Hematol 1988;25:11-6.
9. Solal-Céligny P, Lepage E, Brousse N, Tendler CL, Brice P, Haioun C, et al. Doxorubicin-containing regimen with or without interferon α-2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial. J Clin Oncol 1998;16:2332-8.
10. Dana BW, Dahlberg S, Nathwani B, Chase E, Coltman C, Miller TP, et al. Long term follow-up of patients with low grade lymphomas treated with doxorubicin based chemotherapy or chemoimmunotherapy. J Clin Oncol 1993;11:644 –51.
11. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-6.
12. Hochster HS, Kim KM, Green MD, Mann RB, Neiman RS, Oken MM, et al. Activity of fludarabine in previously treated non-Hodgkin's low-grade lymphoma: results of an Eastern Cooperative Oncology Group study. J Clin Oncol 1992;10:28-32.
13. Solal-Céligny P, Brice P, Brousse N, Caspard H, Bastion Y, Haioun C, et al. Phase II trial of fludarabine monophosphate as first-line treatment in patients with advanced follicular lymphoma: a multicenter study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1996;14:514-9.
14. Hochster HS, Oken M, Winter J, Gordon LI, Raphael BG, Bennett JM et al. Phase I study of fludarabine plus cyclophosphamide in patients with previously untreated low-grade lymphoma: results and and long-term follow-up: a report from the Eastern Cooperative Oncology Group. J Clin Oncol 2000; 18: 987-94.
15. Hagenbeek A, Eghbali H, Monfardini S, Resegotti E. Fludarabine versus conventional CVP chemotherapy in newly diagnosed patients with stage III and IV low grade malignant non-Hodgkin's lymphoma. Preliminary results from a prospective, randomized phase III clinical trial in 381 patients. Blood 1998;10:1294.
16. Klasa R, Shustik C, Sawka C, Smith A, Grenier JF, Berube S. Phase III trial comparing fludarabine to CVP in patients with recurrent low grade, non-Hodgkin's lymphomas. Ann Oncol 1999;10:220[abstract].
17. McLaughlin P, Hagemeister FB, Romaguera JE, Sarris AH, Pate O, Younes A, et al. Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. J Clin Oncol 1996;14:1262-8.
18. Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al. (IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997;90:2188-95.
19. Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, et al. Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1999;10:655-61.
20. Nguyen DT, Amess JA, Doughty H, Hendry L, Diamond LW. IDEC-C2B8 anti-CD20 (rituximab) immunotherapy in patients with low-grade non-Hodgkin's lymphoma and lymphoproliferative disorders: evaluation of response on 48 patients. Eur J Haematol 1999;62:76-82.
21. Davis TA, White CA, Grillo-Lopez AJ, Velasquez WS, Link B, Maloney DG, et al. Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. J Clin Oncol 1999;17:1851-7.

22. Foran JM, Gupta RK, Cunningham D, Popescu RA, Goldstone AH, Sweetenham JW, et al. A UK multicentre phase II study of rituximab (chimaeric anti-CD20 monoclonal antibody) in patients with follicular lymphoma, with PCR monitoring of molecular response. Br J Haematol 2000;109:81-8.
23. Case D, Ebrahim JK, Hedlund J, Boyd M, Aronson F, Hayes D. Rituximab in relapsed follicular lymphoma. Blood 1999;94:a [abstract 4704].
24. Feuring-Buske M, Kneba M, Unterhalt M, Engert A, Gramatzki M, Hiller E, et al. IDEC-C2B8 (Rituximab) anti-CD20 antibody treatment in relapsed advanced-stage follicular lymphomas: results of a phase-II study of the German Low-Grade Lymphoma Study Group. Ann Hematol 2000;79:493-500.
25. Ghielmini M, Schmitz SF, Burki K, Pichert G, Betticher DC, Stupp R, et al. The effect of Rituximab on patients with follicular and mantle-cell lymphoma. Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol 2000;11 Suppl 1:123-6.
26. Walewski J, Kraszewska E, Mioduszewska O, Romejko-Jarosinska J, Hellmann A, Czyz J, et al. Polish Lymphoma Research Group. Rituximab (Mabthera, Rituxan) in patients with recurrent indolent lymphoma: evaluation of safety and efficacy in a multicenter study. Med Oncol 2001;18:141-8.
27. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-63.
28. McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-33.
29. Hiddemann W, Forstpointner R, Fiedler F, Gramatzki M, Dörken B, Illiger HJ, et al. Combined immuno-chemotherapy (R-FCM) is superior to a Fludarabine-containing regimen (FCM) alone in recurrent follicular and mantel cell lymphomas- results of a prospective randomized comparison of the German Low Grade Study Group (GLSG). ICML 2002;186a[abstract].
30. Herold M, Fiedler F, Pasold R, Knauf W, Freund M, Naumann R, et al. Efficacy and toxicity of rituximab plus MCP versus MCP alone in advanced indolent NHL - interim results of a clinical phase III study of the East German Study Group Hematology/Oncology (OSHO). ICML 2002;511a[abstract].
31. Sacchi S, Tucci A, Merli F, Orsucci L, Cervetti G, Occhini U, et al. Phase II study with fludarabine and cyclophosphamide plus rituximab (FC+R) in relapsed follicular lymphoma patients. Blood 2002;100:2246a[abstract].
32. Weide R, Heymanns J, Pandorf A, Koeppler H. Bendamustine/mitoxantrone/rituximab (BMR): a new effective treatment for refractory or relapsed indolent lymphomas. Blood 2002;100: 2247a[abstract].
33. Ogura M, Kikuchi A, Kawase T, Kajimoto K, Kamiya Y, Taji H, et al. Phase I/II study of a new salvage chemotherapy with rituximab (CHASER therapy) for relapsed advanced follicular lymphoma (FL) and mantle cell lymphoma (MCL). Blood 2002;100:4713a[abstract].
34. Amar-Maman D, Mounier N, Manson J, Vignot S, Brice P, Briere J, et al. Evaluation of efficacy and toxicity of rituximab plus aracytin-platinum (R-DHAP) regimen in non-Hodgkin lymphoma (NHL) relapsing patients. Blood 2002;100: 4710a [abstract].
35. Komaba S, Tashiro H, Noguchi M, Sanaka T, Gotoh M, Kawasugi K, et al. ESHAP plus RITUXIMAB (ESHAP-R) regimen for relapsing or refractory non-Hodgkin's lymphoma (NHL): study of four cases. Blood 2002;100:a4746[abstract].
36. Davis TA, Maloney DG, Grillo-Lopez AJ, White CA, Williams ME, Weiner GJ, et al. combination immunotherapy of relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma with rituximab and interferon-α-2a. Clin Cancer Res 2000; 7:2644–52.
37. Bron D, Van Den Neste E, Vandengerghe P, Van Hoof A, Van Droogenbroeck J, De Bock R, et al. Mabthera followed by Roferon induces prolonged responses in patients with refractory/relapsing low grade or follicular lymphomas. A phase II study from the Belgian Hematological Society. ICML 2002; a509[abstract].
38. Sacchi S, Federico M, Vitolo U, Boccomini C, Vallisa D, Baldini L, et al; GISL. Clinical activity and safety of combination immunotherapy with IFN-α 2a and Rituximab in patients with relapsed low grade non-Hodgkin's lymphoma. Haematologica 2001;86:951-8.
39. Kymby E. Beyond immunochemotherapy: combinations of rituximab with cytokines interferon-α2a and granulocyte colony stimulating factor. Semin Oncol 2002;29:2 Suppl 6:7-10.
40. Friedberg JW, Neuberg D, Gribben JG, Fisher DC, Canning C, Koval M, et al. Combination immunotherapy with rituximab and interleukin 2 in patients with relapsed or refractory follicular non-Hodgkin's lymphoma. Br J Haematol 2002; 117: 828-34.
41. Ansell SM, Witzig TE, Kurtin PJ, Sloan JA, Jelinek DF, Howell KG, et al. Phase 1 study of interleukin-12 in combination with rituximab in patients with B-cell non-Hodgkin lymphoma. Blood 2002;99:67-74.
42. McLaughlin P, Rodriguez MA, Reuben J, East K, Grimm E, Hagemeister FB, et al. Rituximab in combination with GM-CSF (leukine) for patients with recurrent indolent lymphoma. Blood 2001;98:2536a[abstract].
43. Rossi JF, Yang LZ, Quittet P, Navarro R, Legouffe E, Fegueux N, et al. Rituximab (Rab) and GM-CSF, an effective therapy for relapsed/refractory patients (pts) with low-grade B-cell lymphoma (L): correlation between response and dendritic cell (DC) subpopulation mobilized. Blood 2001;98:2542a [abstract].
44. Redfern C, Guthrie TH, Smith MR, Adler M, Holman P, Leonard JP, et al. A phase II trial of Favid™ [Id-KLH] for relapsed indolent non-Hodgkin's lymphoma. Blood 2002;99:1383a [abstract].
45. T Hayashi, Kenneth C. Anderson, Steven P. Treon. rituximab induced antibody dependent cell mediated cytotoxicity (ADCC) is enhanced by thalidomide and its analogue revimid. Blood 2002;100:4800a[abstract].
46. Hegde U, White T, Stetler-Stevenson M, Marti G, Janik J, Pittaluga S, et al. phase I study of combination Rituximab (CD20) and Apolizumab (Hu1D10) monoclonal antibody therapy in previously treated B-cell lymphoma and chronic lymphocytic leukemia. Blood 2002;100:1389a[abstract].
47. Grillo-Lopez AJ. A model for the breadth and depth of clinical effect observed with Rituximab and Zevalin in NHL patients. Blood 2002;100:a4780[abstract].
48. Hainsworth JD, Litchy S, Burris HA 3rd, Scullin DC Jr, Corso SW, Yardley DA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. J Clin Oncol 2002;20:4261-7.
49. Solal-Céligny P, Salles G, Brousse P, Soubeyran P, Delwail V, Deconninck E, et al. Updated results of rituximab as single first-line therapy for patients with follicular lymphoma (FL) and a low tumor burden: clinical and molecular evaluation. ICML 2002;a506[abstract].
50. Witzig TE, Vukov AM, Habermann TM, Geyer S, Friedenberg WR, White WL, et al. Rituximab therapy for patients with newly diagnosed, asymptomatic advanced-stage follicular grade I non-Hodgkin's lymphoma (NHL): a phase II trial in the North Central Cancer Treatment Group (NCCTG). Blood 2002; 100: a1398[abstract].
51. Ferrari D, Girmenia G, Brunati S, Rosato E, Montillo M. Successful response to rituximab as a single agent in bulky disease follicular lymphoma. Blood2002;100:a4783[abstract].
52. Emmanouilides CR. Rituximab-mediated sensitization of B-non-Hodgkin's lymphoma (NHL) to cytotoxicity induced by paclitaxel, gemcitabine, and vinorelbine. Cancer Biother Radiopharm 2002;17:621-30.
53. Czuczman M, Fallon A, Mohr A, Carleton S, Bernstein ZP, McCARTHNY p, et al. Rituximab in combination with CHOP or fludarabine in low-grade lymphoma. Semin Oncol 2002;29 Suppl 2:36-40.
54. Maloney DG, Press OW, Braziel RM, Unger JM, LeBlanc ML, Grogan TM, et al. A phase II Trial of CHOP followed by rituximab chimeric monoclonal anti-CD20 antibody for treatment of newly diagnosed follicular non-Hodgkin's lymphoma: SWOG 9800. Blood 2001;98:a3502[abstract].
55. Jaeger G, Neumeister P, Brezinschek R, Hofler G, Quehenberger

F, Linkesch W, Sill H. Rituximab (anti-CD20 monoclonal antibody) as consolidation of first-line CHOP chemotherapy in patients with follicular lymphoma: a phase II study. Eur J Haematol 2002;69:21-6.
56. Zinzani PL, on Behalf of an Italian Cooperative Study Group on Lymphoma. A multicenter randomized trial of fludarabine and mitoxantrone (FM) plus rituximab versus CHOP plus rituximab as first-line treatment in patients with follicular lymphoma (FL). Blood 2001;98:a344[abstract].
57. Czuczman MS, Fallon A, Mohr A, Stewart C, Klippenstein D, Loud P, et al. Phase II Study of Rituximab Plus Fludarabine in Patients (pts) with Low-Grade Lymphoma (LGL): Final Report. Blood 2001;98a2518[abstract].
58. Vitolo U, Boccomini C, Astolfi M, Ladetto M, Rota-Scalbrini D, Pogliani E, et al. High clinical and molecular response rate in elderly patients with advanced stage follicular lymhoma treated at diagnosis with a brief chemo-immunotherapy FND + rituximab. Blood 2002;98:a1392[abstract].
59. Cohen A, Polliack A, Ben-Bassat I, Avigdor A, Bennett M, Berkowicz M, et al. Results of a phase ii study employing a combination of fludarabine, cyclophosphamide and Rituximab (FCR) as primary therapy for patients with advanced follicular lymphoma (FL): The Israel Cooperative Lymphoma Group. Blood 2002;100a1393[abstract].
60. Gregory SA, Venugopal P, Adler S, Enschede S, Yunus F, O'Brien T, et al. Combined fludarabine, mitoxantrone, and Rituximab achieves a high response as initial treatment for advanced low grade non-hodgkin's lymphoma (LGNHL). Blood 2002;100a 1401[abstract].
61. Rubio-Borja ME, Tripp FJ, Baez E, Rivas S, Rubio B, Baltasar S. CNOP vs CNOP-R vs Ruximab monotherapy as first-line therapy for indolent non-Hodgkin lymphoma (I NHL). A preliminary report from the Mexican Multicentric Hematology Study Group. Blood 2002;100:a4794[abstract].
62. Odaimi M, Rubin A, Ahern K, Lee R, Basile M, Terjanian T, et al. Interim results of a phase II trial of therapy with cyclophosphamide/pentostatin/ Rituximab for indolent NHL and CLL. Blood 2002;100:a4797[abstract].
63. Martinelli G, Laszlo D, Mancuso P, Santoro P, Pruneri G, Vanazzi A, et al. Rituximab plus chlorambucil in low-grade non Hodgkin's lymphomas (NHL): clinical results of a phase II study. Blood 2002;100:a3073[abstract].
64. Igarashi T, Ohtsu T, Fujii H, Sasaki Y, Morishima Y, Ogura M, et al. IDEC-C2B8 Study Group. Re-treatment of relapsed indolent B-cell lymphoma with rituximab. Int J Hematol 2001; 73:213-21.
65. Davis TA, Grillo-Lopez AJ, White CA, McLaughlin P, Czuczman MS, Link BK, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. J Clin Oncol 2000;18:3135-43.
66. Coiffier B, Bouaffia F, Thieblemont C, Hequet O, Arnaud P, Dumontet C, et al. Rituximab re-treatment in B-cell lymphoma patients: efficacy and toxicity in 59 patients treated in one center. Blood 2002;100:a1390[abstract].
67. Cohen Y, Libster D, Da'as D, Amir G, Polliack A. Re-treatment with rituximab alone induces sustained remission in a patient with follicular lymphoma with multiple extranodal sites of involvement, relapsing soon after primary treatment with fludarabine-rituximab. The Hematology Journal 2003;4:151-3.
68. Ghielmini M, Schmitz SFH, Cogliatti S, Pichert G, Fey M, Betticher D, et al. Lymphoma Working Group, Swiss Group for Clinical Cancer Research (SAKK). Prolonged treatment with rituximab significantly improves event free survival and duration of response in patients with follicular lymphoma: a randomised SAKK trial. Blood 2002;100:a604[abstract].
69. Gordan L, Grow WB, Braylan RC, Mendenhall NP, Douglas V, Pusateri A, et al. A phase II trial of individualized pharmacokinetic dosing of rituximab maintenance for patients with CD-20 positive lymphoproliferative disorders. Blood 2002;100: a1400[abstract].
70. Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. N Engl J Med 2001;4:344:68-9.
71. Schmitz K, Brugger W, Weiss B, Kaiserling E, Kanz L. Clonal selection of CD20-negative non-Hodgkin's lymphoma cells after treatment with anti-CD20 antibody rituximab. Br J Haematol 1999;106:571-2.
72. Davis TA, Czerwinski DK, Levy R. Therapy of B-cell lymphoma with anti-CD20 antibodies can result in the loss of CD20 antigen expression. Clin Cancer Res 2000;6:317-8.
73. Leo E, Scheuer L, Kraemer A, Kerowgan M, Leo A, Anthony D. Unexpected hematotoxicity associated with a combination of Rituximab, fludarabine and cyclophosphamide in the treatment of relapsed follicular lymphoma. Blood 2002;100: a4745 [abstract].
74. Jilani I, O'Brien S, Manshouri T, Thomas DA, Thomazy VA, Imam M, et al. Transient Downmodulation of CD20 by rituximab. Blood 2002;100:a3174[abstract].
75. Seliem RM, Freeman JK, Hasserjian RP. Modulation of CD20 expression in B-cell lymphomas treated with Rituximab. Blood 2002;100:a4787[abstract].
76. Kennedy GA, Tey SK, Cobcroft R, Marlton P, Grimmett K, Gill D. Incidence and nature of CD20 negative relapses following Rituximab therapy in aggressive B-cell non-Hodgkin's lymphoma: a retrospective review. Blood 2002; 100:a1394 [abstract].
77. Savage KJ, Weng AP, Kutok JL, Pinkus G, Gribben JG. Loss of CD20 expression following treatment with anti-CD20 monoclonal antibody in chronic lymphocytic leukemia. Blood 2002;100:a5013[abstract].
78. Cohen Y, Da'as N, Libster D, Amir G, Berrebi A, Polliack A. Large cell transformation of chronic lymphocytic leukemia and follicular lymphoma during or soon after treatment with fludarabine-rituximab containing regimens: natural history or therapy related complication? Eur J Haematol 2002;68:1-9.
79. Finke J, Slanina J, Lange W, Dolken G. Persistence of circulating t(14;18)-positive cells in long-term remission after radiation therapy for localized-stage follicular lymphoma. J Clin Oncol 1994;12:798-805.
80. Price CG, Meerabux J, Murtagh S, Cotter FE, Rohatiner AZ, Young BD, et al. The significance of circulating cells carrying t(14;18) in long remission from follicular lymphoma. J Clin Oncol 1993;11:1668-73.
81. Lambrechts AC, Hupkes PE, Dorssers LC, van't Veer MB. Clinical significance of t(14; 18)-positive cells in the circulation of patients with stage III or IV follicular non-Hodgkin's lymphoma during first remission. J Clin Oncol 1994;12:1541-6.
82. Mandigers CM, Meijerink JP, Mensink EJ, Tonnissen EL, Hebeda KM, Bogman MJ, et al. Lack of correlation between numbers of circulating t(14;18)-positive cells and response to first-line treatment in follicular lymphoma. Blood 2001 15;98:940-4.
83. Rambaldi A, Lazzari M, Manzoni C, Carlotti E, Arcaini L, Baccarani M, et al. Monitoring of minimal residual disease after CHOP and rituximab in previously untreated patients with follicular lymphoma. Blood 2002;99:856-62.
84. Freedman AS, Neuberg D, Mauch P, Soiffer RJ, Anderson KC, Fisher DC, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. Blood 1999;94:3325-33.
85. Hirt C, Dolken G. Quantitative detection of t(14;18)-positive cells in patients with follicular lymphoma before and after autologous bone marrow transplantation. Bone Marrow Transplant 2000;25:419-26.
86. Zwicky C, Maddocks A, Andersen N, Gribben J. Eradication of polymerase chain reaction detectable immunoglobulin gene rearrangement in non-Hodgkin's lymphoma is associated with decreased relapse after autologous bone marrow transplantation. Blood 1996;88:3314-22.
87. Salles G, Coiffier B. Autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. Baillieres Best Pract Res Clin Haematol 1999;12:151-69.
88. Johnson PW, Price CG, Smith T, Cotter FE, Meerabux J, Rohatiner AZ, et al. Detection of cells bearing the t(14;18) translocation following myeloablative treatment and autologous bone marrow transplantation for follicular lymphoma. J Clin Oncol 1994;12:1685-92.
89. Ladetto M, Volpato F, Drandi D, Compagno M, Astolfi M, Mantoan B, Vallet S, Ricca I, Corradini P, Boccadoro M, Tarella C. Frequent detection of rearrangements unrelated to those observed at diagnosis in late molecular recurrences of follicular lymphoma (FL) patients. Blood 2002;100:a2220[abstract].

90. Sarris AH, Jiang Y, Tsimberidou AM, Thomaides A, Rassidakis GZ, Ford RJ, et al. Quantitative real-time polymerase chain reaction for monitoring minimal residual disease in patients with advanced indolent lymphomas treated with rituximab, fludarabine, mitoxantrone, and dexamethasone. Semin Oncol 2002;29 1 Suppl 2:48-55.
91. Horning SJ, Negrin RS, Hoppe RT, Rosenberg SA, Chao NJ, Long GD, et al. High-dose therapy and autologous bone marrow transplantation for follicular lymphoma in first complete or partial remission: results of a phase II clinical trial. Blood 2001;97:404-9.
92. Freedman AS, Neuberg D, Mauch P, Soiffer RJ, Anderson KC, Fisher DC, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. Blood 1999;94:3325-33.
93. Ladetto M, Corradini P, Vallet S, Benedetti F, Vitolo U, Martelli M, et al. High rate of clinical and molecular remissions in follicular lymphoma patients receiving high-dose sequential chemotherapy and autografting at diagnosis: a multicenter, prospective study by the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Blood 2002;100:1559-65.
94. Martin S, Fischer C, Niederste-Hollenberg A, Free M, Meckenstock G, Haas R, et al. Eradication of minimal residual disease in patients with follicular lymphoma depends on the disease status and the type of cytotoxic therapy combined with the anti-CD20 monoclonal antibody (rituximab) as revealed by molecular monitoring with nested and real-time PCR. Blood 2002;100:a1395[abstract].
95. Emmanouilides C, Lill M, Rosenfelt F, Abdelkedous S, Telatar M, Grody W, et al. Mine-Rituxan salvage and in vivo purging in patients with lymphoma. Blood 2001;98: abstract3077 [abstract].
96. Buckstein RJ, Imrie KR, Spaner D, Mangel J, Tompkins K, Crump M, et al. Autologous stem cell transplants combined with rituximab for relapsed follicular lymphoma achieve prolonged clinical and molecular remissions. Blood 2001;98:a2846[abstract].
97. Ladetto M, Zallio F, Vallet S, Ricca I, Cuttica A, Caracciolo D, et al. Concurrent administration of high-dose chemotherapy and rituximab is a feasible and effective chemo/immunotherapy for patients with high-risk non-Hodgkin's lymphoma. Leukemia 2001;15:1941-9.
98. Buckstein RJ, Rimrie K, Pennell N, Spaner D, Hewitt K, Berinstein NL. Prolonged molecular and clinical remission after treatment of a patient with follicular lymphoma with rituximab. Leuk Lymphoma 2001;41:451-5.
99. Flinn IW, Jones RJ, Goodrich A, Carter-Brookins D, Moss TJ, Loper K, et al. Rituximab during autologous stem cell transplantion for lymphoma produces lymphoma free grafts in most patients by PCR and clonogenic assays. Blood 2001;98:a2832 [abstract].
100. Flohr T, Hess G, Kolbe K, Gamm H, Nolte H, Stanislawski T, et al. Rituximab in vivo purging is safe and effective in combination with CD34-positive selected autologous stem cell transplantation for salvage therapy in B-NHL. Bone Marrow Transplant 2002;29:769-75.
101. Lazzarino M, Arcaini L, Bernasconi P, Alessandrino EP, Gargantini L, Cairoli R, et al. A sequence of immuno-chemotherapy with rituximab, mobilization of in vivo purged stem cells, high-dose chemotherapy and autotransplant is an effective and non-toxic treatment for advanced follicular and mantle cell lymphoma. Br J Haematol 2002;116:229-35.
102. Mangel J, Buckstein R, Imrie K, Spaner D, Franssen E, Pavlin P, et al. Pharmacokinetic study of patients with follicular or mantle cell lymphoma treated with rituximab as in vivo purge and consolidative immunotherapy following autologous stem cell transplantation. Blood 2002; 100:a5498 [abstract].
103. Leonard JP, Coleman M, Matthews JC, Dosik A, Fiore JM, Kapushok H, et al. High complete response rate following Epratuzumab (anti CD22) and rituximab (anti CD-20) combination antibody therapy in follicular non-Hodgkins lymphoma (NHL). ICML 2002;a111[abstract].
104. Ladetto M, Ricca I, Benedetti F, Vitolo U, Liberati M, Musso M, et al. Multicenter prospective randomized GITMO trial comparing high dose sequential chemotherapy with autografting and CHOP both supplemented with rituximab as frontline therapy for high-risk follicular lymphoma (FL) patients: an interim analysis. Blood 2002;100:a4769 [abstract].
105. Brugger W, Hirsch J, Repp R, Grünebach F, Schlimok G, Vogel W, et al. Treatment of follicular and mantle cell lymphoma with rituximab after high-dose chemotherapy and autologous blood stem cell transplantation: a multicenter phase ii study. Blood 2002;100:a2532[abstract].
106. Buckstein RJ, Mangel J, Imrie K, Spaner D, Crump M, Pennell N, et al. High dose therapy/ASCT consolidated with rituximab and or α interferon immunotherapy for relapsed follicular lymphoma prolongs PFS and achieves durable molecular remissions. Blood 2002;100:a2547[abstract].
107. Blum KA, Hidalgo J, Khoury H, Baty J, Brown RA, Adkins DR, et al. Delayed neutrophil and platelet engraftment following autologous transplantation in non-Hodgkins lymphoma patients previously treated with rituximab. Blood 2002;100: a2531[abstract].
108. Hidalgo KA. Blum KA, Adkins D, Brown R, Devine S, Mayfield J, et al. Impact of pre-transplant rituximab on early post-transplant complications in NHL. Blood 2002;100:a5313 [abstract].
109. Buckstein R, Imrie K, Spaner D, Potichnyj A, Robinson JB, Nanji S. Stem cell function and engraftment is not affected by "in vivo purging" with rituximab for autologous stem cell treatment for patients with low-grade non-Hodgkin's lymphoma. Semin Oncol 1999;26: Suppl 14:115-22.
110. Buckstein RJ, Mangel J, Imrie KR, Spaner D, Boudreau A, Crump M, et al. Immunoglobulin recovery following high dose therapy and post-ASCT rituximab for relapsed follicular lymphoma (FL) and newly diagnosed mantle cell lymphoma (MCL) compared to standard dose chemotherapy. Blood 2002;100: a5502[abstract].
111. Dillman RO, Chico S. Low-grade lymphomas: comparison of histologic classifications and survival rates for patients diagnosed during the last two decades. Blood 2002;100:a4631 [abstract].
112. Hirt C, Schueler F, Schwenke C, Kiefer T, Herold M, Dolken G. High percentage of molecular remissions in advanced stage follicular lymphoma (FL) patients treated with chemoimmunotherapy in comparison to chemotherapy alone. Blood 2002;100:a1402[abstract].

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Gilles Salles, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Salles and the Editors. Manuscript received April 17, 2003; accepted May 20, 2003.

Disclosures

Dr. Yossi Cohen and Professor Aaron Polliack have no financial relationships with pharmaceutical companies; Philippe Solal-Céligny received an honorarium in 2002 from Roche Canada for several presentations.