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Malignant Lymphomas

Rituximab monotherapy for splenic marginal zone lymphoma

In this retrospective study, rituximab was found to be effective therapy in 10 of 11 patients with splenic marginal zone lymphoma, inducing prompt reduction in splenomegaly, improvement in blood counts in 9 patients and clearance of a pleural effusion in 1 patient. Median response duration was 21 months (range 4 to 37 months). Two patients who relapsed at 21 and 23 months responded to retreatment. Rituximab should be considered in patients who are poor candidates for splenectomy.

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Splenic marginal zone lymphoma (SMZL) is accepted within the WHO classification as an indolent disease with distinct clinical, morphological and immunophenotypic features.[1,2] Patients typically have splenomegaly, inconspicuous lymphadenopathy, and circulating neoplastic cells characterized by unipolar cytoplasmic projections, round or oval nuclei and clumped chromatin. The lymphoma cells express CD19, CD20, and CD22 but not usually CD5, CD10, CD23, CD25, CD43, CD103 or cyclin D1.[3] No treatment may be necessary at the outset. In initially untreated patients the 5-year survival rate has been reported to be 88%.[4] Although no standard therapy has yet been established, splenectomy is considered the treatment of choice giving a significant survival advantage over chemotherapy.[5]

We treated 11 patients with the anti-CD20 chimeric monoclonal antibody rituximab at a dose of 375 mg/m^2 once a week for 4 consecutive weeks and retrospectively reviewed these patients' records.

The diagnosis of SMZL was based on clinical features, cell morphology and an immunofluorescent phenotype which excluded other types of lymphoid malignancy (Table 1). Ten patients had enlarged spleens palpable between 6 and 21 cm below the costal margin and were treated because of cytopenias and symptomatic splenomegaly. One patient (#9) had had a splenectomy three months previously and was treated because of a persistent symptomatic exudative pleural effusion. Nine patients had had previous chemotherapy with prednisone, chlorambucil, fludarabine, or cyclophosphamide. Rituximab was chosen because the patients were considered poor candidates for surgery or had refused surgery. A complete hematologic response was defined as the absence of a palpable spleen, disappearance of villous lymphocytes from the peripheral blood and normalization of the complete blood count. A partial response was defined as at least a 50% decrease in spleen size and improvement in blood counts. Bone marrow was not re-examined. All patients tolerated rituximab infusions without serious side effects such as tumor lysis syndrome. Ten of the 11 responded. Nine of the 10 patients with splenomegaly had an initial rapid reduction in spleen size followed by a slower decrease, resulting in an impalpable or barely palpable spleen in 2 to 34 weeks (median 16 weeks) accompanied by improvement in blood counts and disappearance of villous lymphocytes. The pleural effusion in patient #9 cleared completely leaving minimal blunting of the left costal margin within 3 months. Eight of the 10 responding patients had complete resolution of their cytopenias (Table 2). Two patients had persistent mild thrombocytopenia, although their spleens were barely palpable. Patient #5 did not respond and later underwent splenectomy. She developed a post-operative pancreatic fistula which took some months to heal, but now remains well with improved blood counts.

In 8 of the 10 responders there has been no evidence of disease progression after a median follow-up of 21 months (range 4-37). Patient #1 was successfully retreated with a second course of rituximab at 21 months because of recurrent progressive splenomegaly and anemia. She was then aged 93 and tolerated the therapy very well. Patient #7 was also successfully retreated at 23 months because of anemia, splenomegaly and night sweats.

As the neoplastic cells in SMZL express CD20 strongly, response to rituximab seemed likely. Indeed, a gratifying response was obtained to rituximab given as a single agent in this series, even in a nonagenarian who could tolerate few other treatment modalities. A previous abstract reported a comparable experience with rituximab in 14 patients described as having splenic lymphoma with villous lymphocytes or marginal zone lym-

Table 1. Clinical features of the patients and their previous treatment.

No.	Age	Sex	Blood	BM	Nodes	Spleen	Previous Treatment
1a*	91	F	+	+	–	16	chlorambucil & prednisone
1b	93		+		–	18	rituximab
2	51	F	+	+	–	15	chlorambucil & prednisone
3	78	F	+	+	–	20	chlorambucil & prednisone
4	72	M	+	+	–	6	chlorambucil & prednisone
5	73	F	+	+	–	21	chlorambucil & prednisone
6	47	M	+	+	–	7	chlorambucil & prednisone
7a*	55	M	+	–	+#	14	none
7b	57		+		+#	14	rituximab
8	85	M	+	–	–	11	prednisone, fludarabine cyclophosphamide
9	75	M	+	+	–	–	splenectomy
10	79	M	–	+	–	15	none
11	79	F	+	+	–	6	chlorambucil & prednisone

*No : patient number Age : in years Blood : presence of villous lymphocytes in peripheral blood; BM : Bone marrow involvement; Nodes : significant lymphadenopathy Spleen : cm below the costal margin; *1a and 7a : features prior to first treatment; 1b and 7b : features prior to second treatment; #2 cm periaortic node which responded to each course of rituximab.*

Table 2. Response to rituximab.

Patient No.	Prior to therapy					After therapy						Time to disease progression
	Spleen size cm*	Hb g/dL	Neu $\times10^9$/L	Lym $\times10^9$/L	Plts $\times10^9$/L	Spleen size cm*	Hb g/dL	Neu $\times10^9$/L	Lym $\times10^9$/L	Plts $\times10^9$/L	Progression free (months)	
1a**	16	9.5	2.82	1.04	76	0	15.0	4.41	1.41	157	11	21
1b	18	9.7	2.96	3.72	123	0	12.7	4.72	1.89	157	4	
2	15	10.9	1.12	0.45	81	0	14.4	4.18	1.07	163	24	
3	20	9.5	3.08	18.6	150	0	13.1	4.4	2.89	178	37	
4	6	9.3	5.18	2.17	82	1	13.4	5.24	1.67	165	13	
5	21	12.1	1.62	3.98	77	20	12.1	2.16	2.36	96		
6	7	12.1	3.33	21.7	209	0	15.8	5.89	2.43	190	10	
7a**	14	12.5	4.4	3.2	169	0	16.3	3.9	1.6	222	19	23
7b	14	13.5	3.2	2.3	166	0	15.2	5.4	1.8	239	4	
8	11	11.3	2.0	3.0	112	1	12.3	5.75	0.6	123	36	
9	-#	13.6	4.6	7.2	299	-	14.8	3.5	4.2	210	29	
10	15	12.9	0.8	1.1	83	0	15.5	4.1	1.6	109	17	
11	6	9.4	3.3	8.23	210	0	11.7	3.62	1.37	244	4	

**cm below the left costal margin; **1a and 7a first treatment course; 1b and 7b second treatment course after relapse; # splenectomy before therapy; Hb, hemoglobin; Neu, neutrophils; Lym, lymphocytes; Plts, platelets.*

phoma.[6] Eight patients responded completely, 3 had a partial response and 3 did not respond. No relapses occurred in the complete responders after a median follow-up of 10 months. In our cases, 8 of the responses were complete and the median progression-free survival of those who did not relapse is 21 months (range 4 to 37 months). The two relapses were both successfully retreated and the second responses continue at 4 months. In another recent report,[7] there was a complete response to rituximab, vincristine and cyclophosphamide in three patients previously resistant to CHOP. Our experience suggests that a trial of rituximab alone should be used before resorting to combination chemotherapy. Not all patients respond to rituximab, but the use of this agent does not preclude subsequent use of other modalities of treatment. Patient 5# was eventually successfully subjected to splenectomy. Our results suggest that rituximab has considerable activity in this indolent lymphoma. It could

replace splenectomy as a good palliative procedure, especially in elderly patients or those with concomitant disease in whom the risks of this procedure are of concern.

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Multiple Myeloma

Correlation between fatigue and hemoglobin level in multiple myeloma patients: results of a cross-sectional study

This cross-sectional study showed a positive correlation between fatigue-related quality of life, evaluated with the FACT-An questionnaire, and hemoglobin level in 1071 patients with multiple myeloma. Multiple regression analysis adjusting for several covariates was used. Improved FACT-An scores in women and men were associated with hemoglobin increase up to sex-specific normal values.

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Anemia is a very common finding in hematologic malignancies including multiple myeloma (MM), and is especially severe in patients with recurrent disease or during chemotherapy.[1] Improved quality of life (QOL) is correlated with increased hemoglobin concentration,[2-6] independently of tumor response.[2,3] The objective of this cross-sectional study was to further examine the relationship between fatigue-related QOL, hemoglobin level and other characteristics in MM patients.

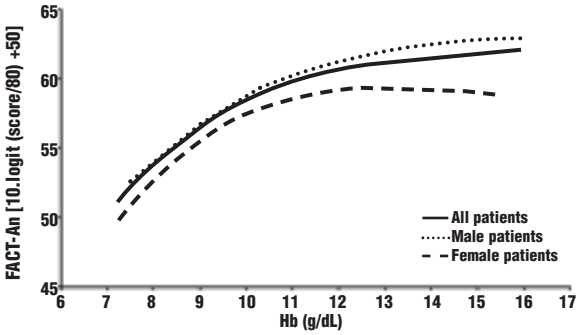

Figure 1. FACT-An scores and hemoglobin levels: multiple logistic regression using third-order polynomials.

All MM outpatients admitted in 24 Italian centers between November 2001 and March 2002 were included. Patients' demographic and clinical data were collected, and the Functional Assessment of Cancer Therapy - Anemia (FACT-An), a 20-item questionnaire measuring fatigue-related QOL,[7] was administered. Raw FACT-An scores were calculated[8] and logit-transformed to obtain approximately normal distributions. The regression of FACT-An scores on hemoglobin was studied using polynomials of increasing order until achieving the maximum adjusted R^2. Other factors, as well as two-way interactions, were tested for addition (if $p<0.05$) into a multiple regression model. Treatment center and its interactions with other model factors (fixed effects) were added as random effects. Data analyses were performed using SAS®.

Of 1071 consecutive patients enrolled, hemoglobin and FACT-An data were available for 1046 (Table 1). The median disease duration was 23 months. MM treatment had previously been administered to 76.6% of the patients and included bone marrow transplant in 31.2%. Treatment was ongoing in 72.0% (chemotherapy with corticosteroids 25.8%, chemotherapy only 11.8%, corticosteroids only 8.5%, interferon 15.7%, thalidomide 10.9%, bisphosphonates 8.4%), while 16.6% were receiving erythropoietin. The mean hemoglobin (Hb) concentration was 11.90 g/dL (SD 1.87, range 6.4-17.0, median 12.0) and 6.1% of the patients were transfusion-dependent. Mean raw FACT-An scores were 56.3 overall (median 60), 36.4 for the fatigue subscale (median 39), and 20.0 for the non-fatigue items (median 21). The FACT-An scale showed good internal consistency (Cronbach's α 0.83). The median raw FACT-An scores increased from 45 for Hb $\geq$ 9 g/dL to 64 for Hb > 14 g/dL. The linear regression coefficient of logit-transformed scores on hemoglobin was 1.36 (standard error 0.135, Pearson's r 0.297, $p=0.0001$). Score improvements per hemoglobin increase were progressively lower, however, and a third-order polynomial best fitted the data (R^2 0.103, i.e. explaining 10.3% of FACT-An score variability versus 8.8% of linear regression). This regression pattern was still observed (Figure 1) after adjusting for other factors (Table 1). The main ($p<0.01$) independent predictors of lower FACT-An scores besides anemia were female sex, older age, unfavorable response, advanced stage and concurrent illness (Table 1). Two-way interactions between factors, including hemoglobin concentration, were not significant. The model R^2