Excel).

Three groups of patients (n=4 per group) were analyzed with non-mutated wild-type FLT3, FLT3-LM, and FLT3-TKD (D835H, D835H, D835Y, del835). The *in vitro* results from each group treated with SU5614 were compared to those of the respective untreated control cells. At the level of clonogenic progenitors (CFC) 2/4 patients with wild-type FLT3, 3/3 with FLT3-LM ($p<0.004$) and 2/2 with FLT3-TKD responded to therapy with as much as 100% reduction of the number of leukemic CFC as compared to the untreated AML cells (Table 1). At the level of HSC (LTC-IC), the compound achieved > 50% cell killing in 3/4 ($p<0.03$) patients with wild-type FLT3, 3/4 with FLT3-LM ($p<0.04$) and 2/4 with FLT3-TKD. The response of both CFC as well as leukemic HSC to SU5614 could not be predicted from the level of expression of FLT3 or the presence of activating mutations or surface expression of c-KIT, a protein tyrosine kinase also targeted by the SU5614 compound (*data not shown*). As a control, $CD34^+$ bone marrow stem cells from healthy donors were analyzed in the same way. At the level of CFC level SU5614 had considerable toxicity, killing a mean (range) of 67.5 % (30-100) of the cells (n=3). In addition, the compound eliminated normal HSC (n=3) with a range between 78 – 100% after 24h incubation. These data demonstrate the efficacy of tyrosine kinase inhibitors at eliminating leukemic stem cells in AML patients with mutated as well as non-mutated FLT3. However, the data also point to a considerable toxicity to normal HSC, which should be taken into account in the management of patients with compromised normal hematopoiesis.

Natalia Arseni,° Farid Ahmed,*° Wolfgang Hiddemann,*° Christian Buske,*° Michaela Feuring-Buske*°*

**GSF, Clinical Cooperative Group Leukemia Grosshadern, Munich, Germany; °Department of Medicine III, Ludwigs-Maximilian University, Munich, Germany*

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Key words: AML, FLT-3, leukemic stem cell, receptor tyrosine kinase inhibitor

Correspondence: Dr. Michaela Feuring-Buske, Department of Medicine III, Klinikum Grosshadern, Marchioninistrasse 15, 81377 Munich, Germany. Phone: international +49.89.7099425. Fax: international +49.89.7099400. E-mail: feuring@gsf.de

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Malignant Lymphomas

Rituximab in patients with mucosal-associated lymphoid tissue-type lymphoma of the ocular adnexa

Eight patients with ocular adnexal mucosal-associated lymphpid tissue (MALT) lymphoma were treated with rituximab, at diagnosis (n=5) or relapse (n=3). All untreated patients achieved lymphoma regression, while relapsing patients had no benefit. Four responding patients experienced early relapse. The median time to progression was 5 months. The efficacy of rituximab in ocular adnexal lymphoma is lower than that reported for gastric MALT lymphomas.

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Any CD20-positive lymphoproliferative disorder is a potentially suitable candidate for treatment with rituximab. Significant rituximab activity has been reported in extranodal mucosal-associated lymphoid tissue (MALT) lymphomas.[2] However, the clinical activity of this drug in MALT lymphomas arising in different organs remains to be defined.[2] MALT-type ocular adnexal lymphoma is a very indolent malignancy that would appear to be a suitable candidate for treatment with a drug that has an excellent safety profile, such as rituximab. However, the use of rituximab in this setting has been only anecdotally investigated.[1,3-5]

We report a series of eight patients with MALT-type ocular adnexal lymphoma treated with rituximab, at diagnosis (patients #1 to 5) or relapse (patients #6 to 8) (Table 1). Patients were treated with rituximab 375 mg/m^2, weekly, for four weeks, according to the conventional administration schedule which includes pre-medication. Patients did not receive steroids or any other concomitant antineoplastic therapy. CD20-positivity and MALT lymphoma histotype were confirmed both at diagnosis and relapse in all

cases. All patients had measurable disease in the ocular adnexa, and two had concomitant systemic disease (Table 1). The study conformed to the tenets of the Declaration of Helsinki.

The tolerance to rituximab was excellent. All five patients treated at diagnosis (patients #1 to 5) had an objective response, which was complete in three cases and partial in two (Table 1); however, four of them experienced local relapse and one of these four also had a systemic relapse. Patients treated with rituximab for relapsed lymphoma (patients #6 to 8) did not achieve an objective response. After a median follow-up from rituximab administration of 46 months, treatment had failed in all patients but one (patient #4), with a median time to progression for the entire series of 5 months. All patients are alive at a median follow-up of 62 months.

This is the largest reported experience on patients with MALT-type ocular adnexal lymphoma treated with rituximab as a single agent. This drug has been associated with modest activity in advanced MALT lymphomas,[5] but with a 73% response rate in a phase II trial on different extranodal MALT lymphomas.[1] Consistently with our observations, reported response rates have been significantly higher among previously untreated patients than among relapsing patients. The activity of rituximab has been reported to be similar in gastric and non-gastric MALT lymphomas;[1] however, an analysis according to extranodal site has not been provided, and the median follow-up was 15 months, thus preventing any conclusion being drawn about long-term results.

To date, only one paper focusing on the activity of rituximab in ocular adnexal lymphoma is available.[3] This study included two patients with conjunctival MALT lymphoma that had relapsed after radiotherapy in whom rituximab then achieved durable remissions. The only patient in our series who did not experience relapse after rituximab had a conjunctival lymphoma. In another study,[4] the role of rituximab was investigated in eight patients with ocular adnexal lymphoma of different histotypes, including three patients with MALT lymphoma. In that study,[4] rituximab was used in combination with chemotherapy and/or radiotherapy, thus preventing any conclusion being drawn about the real efficacy of the monoclonal antibody. Consistently with our observations, however, two of the three patients with MALT lymphoma experienced early relapse after rituximab-containing therapy. Anecdotally, rituximab activity has been reported in a few cases of ocular adnexal lymphoma other than of MALT-type; stage, management and follow-up were variable.[4,7,8]

Our experience suggests a discrepancy between the activity and efficacy of rituximab against MALT lymphomas arising in the ocular adnexa and those occurring in the stomach. In fact, despite a high activity in both lymphomas, the efficacy of rituximab against ocular adnexal lymphoma of MALT-type seems to be lower than that reported for gastric MALT lymphoma.[9] In a retrospective series of 26 patients with gastric MALT lymphoma, 77% of the patients responded to rituximab and only two patients had relapses, after a median follow-up of 33 months.[9] These results clearly contrast with the treatment failures observed in seven of our eight patients and the median time to progression of 5 months. These differences in the efficacy of rituximab could be in part explained by the known heterogeneity of extranodal MALT lymphomas, which display a different natural behavior according to the organ in which they arise.[2]

Table 1. Stage, extent of disease, objective response, and duration of response after rituximab.

N.	Sex/ Age	Stage disease	Orbital disease	Systemic	Therapy line#	Objective response*	TTP (mo.)	Site of relapse
1	F/56	IV	lachrymal gland	stomach, mediastinum & axillary lymph n.	1st	CR	23	L
2	F/59	IV	lachrymal gland (bilateral)	–	1st	CR	17	L
3	F/74	I	orbit	–	1st	PR	48	L + S§
4	F/38	I	conjunctiva	–	1st	CR	37+	
5	F/48	I	conjunctiva	–	1st	PR	2	L
6	F/22	I	orbit	–	2nd	PD	0	L
7	F/74	IV	orbit	bone marrow, parotid gland & cervical lymph n.	3rd	PD	0	L
8	M/55	IV	conjunctiva (bilateral)	–	5th	SD	5	L

*No patient had ECOG-PS >1, systemic symptoms or elevated levels of serum lactate dehydrogenase . #Patient #6 had been previously treated with CEOP chemotherapy, patient #7 with CEOP chemotherapy and orbital irradiation, and patient #8 with orbital irradiation, CHOP chemotherapy, doxycycline, and intralesional interferon. *Objective response was defined according to the WHO criteria.[6] CR: complete remission; PR: partial response, PD: progressive disease; SD: stable disease; TTP: the time to progression was calculated from therapy conclusion to the date of lymphoma progression or last date of follow-up; "+" indicates the absence of lymphoma progression after therapy. L: local; S: systemic. Preliminary data concerning patients #1 and 2 have been previously reported.[1] §Systemic relapse consisted of lymphomatous involvement of axillary lymph nodes and subcutaneous nodules.*

In conclusion, rituximab is highly active against newly diagnosed ocular adnexal lymphoma, while it is inefficient in relapsing patients. Its activity is similar to that observed in other extranodal MALT lymphomas, but its long-term efficacy is modest. The relapse rate in patients with ocular adnexal MALT lymphoma is clearly higher than that reported for gastric MALT lymphoma, suggesting that MALT lymphomas arising in different organs could show varied sensitivity to rituximab. Further investigations will be needed to define the best role for rituximab in the management of extranodal MALT lymphomas.

Andrés J.M. Ferreri, Maurilio Ponzoni,° Giovanni Martinelli,# Giuliana Muti,@ Massimo Guidoboni,^ Riccardo Dolcetti,^ Claudio Doglioni°*

Medical Oncology Unit and Pathology Unit, °San Raffaele H Scientific Institute, Milan, Italy; #Division of Hematology, European Institute of Oncology, Milan; @Division of Hematology, IRCCS Niguarda Cà Granda, Milan; ^Immunovirology and Biotherapy Unit, Dept. of Pre-Clinical and Epidemiological Research, Centro di Riferimento Oncologico, IRCCS National Cancer Institute, Aviano, Italy*

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Correspondence: Andrés J.M. Ferreri, MD, Medical Oncology Unit, Dept. of Oncology, San Raffaele H Scientific Institute, Via Olgettina 60, 20132, Milan, Italy. Phone: international +39.02.26437649. Fax: international +39.02.26437603. E-mail: andres.ferreri@hsr.it