Rituximab plus subcutaneous cladribine in patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue: a phase II study by the *Arbeitsgemeinschaft Medikamentöse Tumortherapie*

Marlene Troch,[1,2] Barbara Kiesewetter,[2] Wolfgang Willenbacher,[3] Ella Willenbacher,[3] Armin Zebisch,[4] Werner Linkesch,[4] Michael Fridrik,[5] Leonhard Müllauer,[6] Richard Greil,[1] and Markus Raderer[2]

[1]Department of Internal Medicine III with Hematology, Medical Oncology, Hemostaseology, Infectious Diseases, Rheumatology, Oncologic Center, Paracelsus Medical University Salzburg, [2]Departments of Internal Medicine I, Divisions of Oncology and the Comprehensive Cancer Center and [6]Pathology of the Medical University of Vienna, [3]Department of Internal Medicine V, Hematology and Oncology, Medical University of Innsbruck, [4]Department of Internal Medicine, Division of Hematology, Medical University of Graz, and [5]Department of Internal Medicine, Divison of Oncology, AKH Linz, Austria

ABSTRACT

Currently, there is no standard systemic treatment for extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue. Both rituximab and cladribine have shown some activity in this disease, but the combination has not been tested so far. In view of this, we initiated a phase II study to assess the activity and safety of rituximab and cladribine in patients with histologically verified mucosa-associated lymphoid tissue lymphoma. Treatment consisted of rituximab 375 mg/m^2 i.v. day 1 and cladribine 0.1 mg/kg s.c. days 1 – 4 every 21 days. In case of complete remission after two courses, another two cycles of therapy were administered, while patients with a partial response or stable disease were scheduled to receive six cycles of treatment. Out of 40 evaluable patients (14 female, 26 male), 39 received treatment as scheduled while one patient died before initiation of therapy and was rated as having progressive disease in the intent-to-treat analysis. Twenty-one patients had gastric lymphoma, while 19 suffered from extragastric mucosa-associated lymphoid tissue lymphoma. Side effects consisted mainly of hematologic toxicity including leukopenia, lymphopenia, anemia and thrombocytopenia. Twenty-three patients had a complete remission (58%) and nine had a partial remission (23%) for an overall response rate of 81%, while five had stable disease (13%) and two progressed during therapy. After a median follow-up of 16.7 months (interquartile range: 15.9 – 18.7 months), 35 patients are alive (88%) while four patients have died and one patient withdrew consent and did not allow further follow up. Our data demonstrate that rituximab plus cladribine is active and safe in patients with mucosa-associated lymphoid tissue lymphoma. *ClinicalTrials.gov Identifier: NCT00656812*

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is the third most common subtype of lymphoma, accounting for 7% of all newly diagnosed cases of lymphoma.[1] Due to its fascinating pathogenesis, MALT lymphoma has become the paradigm for a malignancy driven by antigenic stimulation, including infection with *Helicobacter pylori* (HP) or long-standing autoimmune diseases such as Sjögren's syndrome or chronic autoimmune thyroiditis. While initially thought to be a strictly localized disease in the majority of patients, recent findings have shown a relatively high rate of multiorgan involvement as well as (systemic) relapses following local therapy.[2,3]

While systemic treatment approaches had been reserved for patients with disseminated disease in the past, recent years have seen an increased number of trials using systemic approaches also in localized disease, probably because of the biological properties of MALT lymphoma. With regards to the most common localization, i.e. the stomach, a recently published consensus paper on the management of gastric MALT lymphoma highlighted that both radiation and systemic therapy have potential curative properties in the case of non-response to HP-eradication treatment.[4]

Both the anti-CD20 antibody rituximab and the nucleoside analogue 2-chlorodeoxyadenosine (cladribine, 2CdA) are effective drugs in the treatment of B-cell lymphomas and have been tested in patients with MALT lymphomas.[5-7] Although both agents have a favorable toxicity profile, some caveats concerning their use remain, such as suboptimal penetration of rituximab into mucosal structures and the inferior response of non-gastric MALT lymphomas as opposed to gastric disease when using cladribine. As MALT lymphomas show a very indolent clinical course with good response rates to various therapeutic agents, the objective in systemic therapy of MALT lymphoma is to define effective combinations

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Correspondence: markus.raderer@meduniwien.ac.at

with minimal side effects. In view of this, we performed a multicenter study to assess the efficacy and safety of the combination of rituximab plus cladribine in order to overcome potential shortcomings of monotherapy with either of these agents.

Design and Methods

The study was conducted between July 2008 and May 2010 in the five participating centers (Medical University of Vienna, Paracelsus Medical University of Salzburg, Medical University of Innsbruck, Medical University of Graz and the General Hospital of Linz). Patients with histologically verified MALT lymphoma according to the criteria outlined in the recent WHO-classification of lymphoid malignancies[8] were eligible for the study. In patients with localized gastric MALT lymphoma, documented refractoriness of the lymphoma to HP eradication (i.e. no change after a minimum follow-up of 12 months after successful eradication of the bacteria) was a prerequisite for inclusion in the trial. Patients with extragastric MALT lymphoma or HP-negative gastric MALT lymphoma (in terms of histology and serology) were eligible directly.

Patients included in the trial had to be older than 18 years with a WHO performance status ≤2; adequate function of the kidneys (serum creatinine <1.5 mg/dL), liver (total bilirubin <2.0 mg/dL and transaminase level <two times the upper limits of normal) and bone marrow (leukocyte count >$3x10^9$/L, platelet count >$100x10^9$/L) was also a prerequisite for study entry and application of each cycle of therapy.

Patients with severe concomitant diseases including a history of another malignancy within 5 years before potential inclusion in the study, florid infections, psychiatric disorders or peripheral neuropathies were not eligible. For female patients of childbearing age, a pregnancy had to be excluded before inclusion in the trial, and patients were required to use adequate contraception throughout the whole duration of treatment.

The study protocol was approved by the local ethical committees of the participating institutions and registered at *www.clinicaltrials.gov* before being started. All patients gave written informed consent according to institutional guidelines.

Before administration of therapy, patients underwent staging consisting of imaging of orbital and salivary glands (in patients with non-gastric MALT lymphoma) and computed tomography (CT) scans of the thorax and abdomen, while patients with gastrointestinal lymphoma also underwent gastroscopy (plus endosonography if available) and colonoscopy. Blood counts and renal and hepatic parameters were evaluated immediately before each cycle, while nadir levels of leukocytes with differential, platelets, hemoglobin and erythrocytes were also measured on day 10 – 14 of each cycle.

Treatment consisted of rituximab (Mabthera®, Roche Austria) given at a dose of 375 mg/m^2 i.v. on day 1 of each cycle and cladribine (Litak®, Lipomed, Switzerland) at a dose of 0.1 mg/kg administered by s.c. injection on days 1 – 4. Premedication consisted of 1000 mg paracetamol and an antihistaminic drug i.v. before rituximab and a 5-HT3 antagonist (either ondansetron or tropisetron i.v.) immediately before the cladribine. Both rituximab and cladribine were provided free of charge for the trial. Cycles were repeated every 21 days, and restaging was performed after every two cycles of therapy. The primary endpoint of the study was an objective response to therapy. Complete remission (CR), partial response (PR), stable disease and progressive disease were assessed according to RECIST 1.1 criteria.[9] In patients with lymphoma restricted to the stomach, response was assessed by endoscopy with histological sampling according to the histological GELA-criteria[10] for CR, stable disease, responding residual disease and probable minimal residual disease. Secondary endpoints were side effects and time to progression.

Restaging was performed after two courses of therapy; patients with progressive disease were taken off study, while patients with stable disease, PR or CR were scheduled for another two courses of treatment. In patients with CR after four cycles, treatment was stopped, while patients with PR or SD received another two cycles to a maximum of six cycles.

All patients were followed for at least another 12 months by regular follow-up assessments every 3 months. Depending on the initial diagnosis the follow-up assessments comprised gastroscopy plus CT of the thorax and abdomen for gastric MALT lymphoma, CT or magnetic resonance imaging for extragastric MALT lymphoma and colonoscopy plus CT of the thorax and abdomen for intestinal lymphoma.

Results

A total of 43 patients were enrolled in the trial, but three were excluded and replaced according to protocol because, during the initial staging, one was found to have renal cell carcinoma and another was found to have small cell lung cancer, while the third patient was diagnosed with a large cell lymphoma after further pathohistological assessment of the material.

Of the 40 evaluable patients, 26 patients were male and 14 female, with a median age of 61 years (IQR: 47-64). At study entry, all patients had a good performance status, i.e. ECOG PS 0 or 1. Twenty-one patients (53%) had gastric MALT lymphoma while the remaining 19 cases had non-gastric MALT lymphoma including six patients with pulmonary, five with ocular adnexal, four with intestinal and two with salivary gland lymphoma, while one patient each had MALT-lymphoma of the skin and the breast (Table 1). All patients with gastric MALT lymphoma had been pretreated with HP-eradication, while 10/40 patients (25%) had been pretreated with chemotherapy and 4/40 (10%) patients with radiation therapy. In eight patients, surgery had been performed at initial diagnosis for retrieval of tissue leading to the diagnosis. Only two patients had been pretreated with a rituximab-containing regimen. At the time of study entry, nine patients had disseminated MALT lymphoma, while the remaining presented with localized disease.

Of the 40 patients judged evaluable, 23 (58%) had a CR, while nine (23%) achieved a PR, resulting in an overall response rate of 81%. Five out of the 40 patients (13%) had stable disease, while three patients were rated as having progressive disease. Of these latter, one patient developed transformation to diffuse large B-cell lymphoma, one patient progressed after one cycle and one patient died before initiation of treatment and was rated as having progressive disease in the intention-to-treat analysis.

Eighteen of the 21 patients (86%) with gastric MALT lymphoma responded to treatment, with 16 patients (76%) achieving a CR and two patients (10%) a PR. The response rate among patients with non-gastric MALT lymphomas was 74% (14/19 patients) with seven CR and 7 PR. The CR were seen after two cycles in 11 patients (9 in gastric and 2 in non-gastric cases); however, some patients subsequently achieved a CR after completion of six cycles of treatment or up to 3 months after the end of treatment

(7 patients with gastric and 5 patients with non-gastric primary lymphomas).

Seven of nine patients (78%; CR in 5 patients, PR in 2 patients) with advanced stage lymphoma (stage III and IV) responded to treatment and 25 of 31 patients with localized disease (81%; CR in 18 and PR in 7) showed a response. Eighty percent of systemically pretreated patients had a response (8/10 patients; 4 CR, 4 PR); likewise, 80% of previously untreated patients had a response (24/30 patients; 19 CR, 5 PR). The response rates are detailed in Table 2.

Treatment-related toxicities were mainly hematologic, with grade III and IV leukopenia in 11/40 (28%) patients, isolated grade III or IV lymphopenia in 4/40 (10%), and grade III anemia and thrombocytopenia in one patient each. Two patients did, however, develop prolonged severe pancytopenia requiring repeated transfusions of packed erythrocytes in both patients and platelet transfusions in one case, as well as repetitive administration of granulocyte colony-stimulating factor. Bone marrow biopsy was not suggestive of myelodysplastic syndrome. The latter patient died 11 months after finishing treatment due to myocardial infarction with ongoing pancytopenia. The other patient recovered fully normal blood counts 13 months after the last treatment.

Grade III fatigue was documented in one patient. Two patients had a grade III allergic reaction during the initial infusion of rituximab and one of these reactions required hospitalization. However, none of these patients had another serious adverse reaction during the following courses of therapy. As a consequence of diarrhea (grade II) one patient developed grade III renal failure, but recovered fully after treatment. Two patients had herpes zoster reactivation and were hospitalized for treatment. One patient developed pneumonia without underlying leukopenia. One patient showed grade II hypertension resulting in short-term hospitalization (Table 3).

After a median follow-up of 16.7 months (IQR; 15.9 – 18.7 months), one patient has relapsed, with the time to relapse being 8 months. Thus, the median time to progression or time to next treatment has not been reached in our patients. Currently, 35 patients are alive, while four patients have died (one patient from a septic event before administration of therapy, one patient from pneumonia, one due to myocardial infarction, and one because of progression of lymphoma); one patient withdrew consent after completion of therapy and did not allow further follow up.

Discussion

There has recently been an increase in trials of systemic treatment strategies in MALT lymphoma, not only because of the expansion of available drugs effective in other B-cell lymphomas but probably also because of the relapses seen after local therapies used in the past.[2,3] Efficacy data for both rituximab and cladribine are available for B-cell neoplasms and some limited data have also been reported for MALT lymphoma.[5-7] Cladribine is a potent purine nucleoside analogue with cytotoxic effects on both dividing and non-dividing lymphocytes. It is remarkably effective in hairy cell leukemia, with overall response rates of up to 98%, and is currently considered standard therapy in this disease.[6] Apart from hairy cell leukemia, cladribine has also been shown to be highly effective in other B-cell neoplasms including marginal

Table 1. Patients' characteristics.

Age (years)	
Median	61
Interquartile range	47-64
Sex	
Female	14
Male	26
Stage	
I/II	31
III/IV	9
Primary site	
Gastric	21
Non-gastric	19
Prior systemic treatment	
Yes	10
No	30
Elevated lactate dehydrogenase	
Yes	9
No	31
Bulky disease	
Yes	1
No	39
Eastern Cooperative Oncology Group (ECOG) Performance Status	
ECOG PS 0	31
ECOG PS 1	9

Table 2. Response rates.

Response rate	N. of patients (%)
Overall	32 (81)
Partial remission	9 (23)
Complete remission	23 (58)
Gastric MALT lymphoma	21
Overall	18 (86)
Partial remission	2 (10)
Complete remission	16 (76)
Non gastric	19
Overall	14 (74)
Partial remission	7 (37)
Complete remission	7 (37)
Advanced stage	9
Overall	7 (78)
Partial remission	2 (22)
Complete remission	5 (56)
Localized stage	31
Overall	25 (81)
Partial remission	7 (23)
Complete remission	18 (58)
Pretreated patients	10
Overall	8 (80)
Partial remission	4 (40)
Complete remission	4 (40)
Untreated patients	30
Overall	24 (80)
Partial remission	5 (17)
Complete remission	19 (63)

zone lymphomas. In a pivotal trial, high efficacy was seen in a cohort of patients with chemotherapy-naïve gastric MALT lymphoma with an overall response rate of 100%,[5] which was maintained after a median follow-up of 6 years in these patients.

While the role of the chimeric anti-CD20 antibody rituximab in combination with chemotherapies is undisputed in almost all types of B-cell lymphomas, its use in MALT lymphoma is being tested in an ongoing randomized trial and it is currently not approved for this indication in Europe. Although it has been shown to have good palliative potential in patients with MALT lymphoma,[7] various caveats such as suboptimal penetration of the antibody into the gastric mucosa[7] and induction of plasmacytic differentiation[11] have been raised. The latter might lead to resistance of the disease to rituximab-containing therapies, as plasma cells are devoid of CD20 expression.

The combination of the two agents used in our study was also tested in splenic marginal zone lymphoma[12] and was retrospectively analyzed and compared with the use of cladribine as a single agent in marginal zone lymphoma by Oricuolo *et al.* in 2009.[13] Data from 15 patients with extranodal marginal zone/MALT lymphoma were available. However, 12 patients received combination therapy while only three patients were given cladribine alone. There were no statistically significant differences between the effects of the two treatment strategies with regards to either response rate (91.7% *versus* 100%) or relapse rate, but the authors suggested a trend to earlier relapse in patients who did not receive rituximab.[13] However, the small number of patients and the retrospective nature of this series do not allow meaningful conclusions to be drawn for the subgroup of patients with MALT lymphoma out of this cohort of marginal zone lymphomas.

To our knowledge, our study is the first prospective series in which the efficacy of the combination of rituximab and subcutaneous cladribine has been assessed in patients with MALT lymphoma. Our data clearly show that this combination is highly effective, resulting in an overall response rate of 81% with a CR rate of 58% (23 patients) and PR in 23% (9 patients). However, as also seen in trials of cladribine alone,[5] the response rate was higher in patients with gastric MALT lymphomas [86% (18/21 patients) in the intention-to-treat analysis; 90% considering only treated patients; 16 CR and 2 PR] than in patients with non-gastric MALT lymphomas [74% (14/19 patients), 7 CR and 7 PR]. In fact, the CR rate in these latter lymphomas (36%, i.e. 7/19 patients) does not appear to be improved when compared to that in our initial study, in which 45% of patients with non-gastric MALT lymphomas achieved a CR. As already discussed in the literature,[2,5] there are various possible explanations for the apparently superior results in gastric MALT lymphomas including a different biology due to pathogenic mechanisms such as HP infection in gastric MALT lymphomas *versus* autoimmune diseases in non-gastric MALT lymphomas. In addition, it can be speculated that the routine histological assessment of treatment responses in gastric MALT lymphoma might allow a more exact evaluation than radiological methods, which could lead to underreporting of CR due to remnants of scar tissue in, for example, the lung, orbit or lymph nodes. In fact, a prior study from our institution showed that histology is much more accurate in assessing response to therapy in gastric MALT lymphoma than is CT or even endosonography.[14] In addition, fluorodeoxyglucose (^{18}F)-positron emission tomography (CT) is not suitable for distinguishing viable lymphoma because of the substantial rate of false results; indeed, this method is not recommended in current guidelines for patients with MALT lymphoma.[4]

Apart from methodological considerations, these findings again suggest a different clinical course for non-gastric MALT lymphomas, which might in fact constitute a heterogeneous group of lymphomas rather than a single disease entity.

In this context, it is important to state that advanced lymphoma stage as opposed to localized disease was not predictive of response, as the overall response rate of all treated patients with advanced lymphoma stage was 78%, and was very similar to that of patients with localized disease (81%). Given that a significantly higher rate of multiorgan involvement had been previously demonstrated in non-gastric MALT lymphomas, one might speculate that this characteristic could have been responsible for the lower response rate in non-gastric MALT lymphomas.[2] In addition, systemic pretreatment did not appear to be a negative predictor of lymphoma response, because both pretreated and untreated patients had identical overall response rates (8/10 pretreated patients *versus* 24/30 untreated patients).

While a better response rate had been reported for rituximab monotherapy in chemotherapy-naive patients with MALT lymphoma, this had not been substantiated for cladribine,[2] and was also not demonstrated for the combination used in our study. That said, only two patients in the present series had received a rituximab-containing regimen prior to study entry and both had a long standing history of MALT lymphoma with multiple previous treatment lines. Stable disease was the best response achieved in both patients, but as the number of patients is so small and both patients were heavily pretreated, further speculations on the role of prior rituximab treatment cannot be made.

A recent study from our institution indicated that rituximab-containing regimens might lead to selection/overgrowth of monoclonal CD20-negative plasma cells and may thus induce a pronounced plasmacytic differentiation.[11] However, development of refractoriness to treatment due to plasmacytic differentiation was not a problem in our study and also has not been found in patients being given rituximab along with fludarabine. The effects of this latter combination were reported by Salar *et al.*, who studied a cohort of 22 patients with MALT lymphoma. The response rate to the combination in this series

Table 3. Side effects.

Grade III/IV	N. of patients
Hematologic	
Leukopenia	11
Lymphopenia	4
Thrombocytopenia	1
Anemia	1
Pancytopenia	2
Allergic reactions	2
Renal insufficiency	1
Herpes zoster	2
Fatigue	1
Pneumonia	1

was excellent, being 100% including 90% CR.[15]

Furthermore, the combination of rituximab and chlorambucil has been shown to be highly effective in patients with MALT lymphoma, resulting in response rates of up to 100%,[22,23] even in gastric MALT lymphomas positive for t(11;18)(q21;q21), a known negative predictive marker for response to chlorambucil.[16-18] This is not, however, surprising, as it has been shown that the activity of rituximab is not dependent on t(11,18)(q21;q21).

After a median follow up of 16.7 months, one patient relapsed and was given salvage immunochemotherapy which resulted in a CR, while no further therapies had to be administered to the remaining patients.

In our series, side effects were manageable and mainly hematologic with a moderate rate of grade III and IV leukopenia, but no episodes of febrile neutropenia were documented. Two patients developed a prolonged, severe pancytopenia, an already described complication of the use of nucleoside analogues. A myelodysplastic syndrome, which has also been described in the context of cladribine treatment, was ruled out by bone marrow biopsy.[19-21] Although one patient recovered fully without any severe complications and it is not likely that the fatal myocardial infarction of the second patient was in any way related to the pancytopenia, the myelotoxicity of cladribine could be a limiting factor and warrants a prolonged observation period. Two patients had to be hospitalized because of herpes zoster reactivation and one could speculate that patients with a history of infection by this virus might benefit from antiviral prophylaxis.

Taken together the combination of rituximab and cladribine is effective and safe in patients with MALT lymphoma. While this was not a randomized study, the data suggest that the addition of rituximab to cladribine is not particularly beneficial, in terms of remission rates, in patients with MALT lymphoma. Compared to data from an older series, in which the CR rate was 100% in gastric MALT lymphomas and 45% in non-gastric MALT lymphomas,[5] the results in the present series do not appear to be strikingly better and again underscore the difference between gastric and non-gastric MALT lymphomas. However, prospective, randomized trials with long-term follow-up are warranted in order to determine whether the addition of rituximab has an influence on time to next treatment or, ultimately, on survival.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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