Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for treatment of early-stage gastric diffuse large B-cell lymphoma

S. Wöhrrer, A. Püspök, J. Drach, M. Hejna, A. Chott & M. Raderer*

Departments of Internal Medicine I, Division of Oncology and Center of Excellence in Clinical and Experimental Oncology (CLEXO); Internal Medicine IV and Clinical Pathology, University of Vienna, Vienna, Austria

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Background: Diffuse large B-cell lymphoma (DLBCL) of the stomach is a relatively common disease. Recently, chemotherapy consisting of doxorubicin, cyclophosphamide, vincristine and prednisone (CHOP) has been reported as effective treatment for early-stage gastric DLBCL. Given the fact that the application of the CD20 antibody rituximab (R) in addition to CHOP has improved outcomes in nodal DLBCL, we have analysed our experience with application of R-CHOP in patients with early-stage gastric DLBCL.

Patients and methods: Patients with histologically verified early-stage gastric DLBCL undergoing treatment with R-CHOP for initial management were analysed.

Results: Fifteen patients received a total of 79 cycles, with a median of six cycles per patient. All patients responded to therapy, 13 had a complete remission (CR) (87%) and two (13%) a partial remission. All patients in CR, except one who died unrelated to lymphoma, have remained so with a median follow-up of 15 months (range 4–42) after treatment. Subjective tolerance was moderate, and toxicities were mainly haematological, including leukocytopenia WHO grade 3 and 4 in 10 and five patients each. The addition of rituximab to the standard CHOP regimen did not appear to significantly increase toxicity.

Conclusions: Our data indicate that R-CHOP is an effective regimen for management of early-stage gastric DLBCL. However, given the excellent results with CHOP alone in such patients, the value of adding rituximab to standard CHOP remains to be determined in a randomised trial.

Key words: chemotherapy, diffuse large B-cell lymphoma, gastric lymphoma, rituximab

Introduction

Extranodal lymphomas occur most commonly in the stomach, with the large majority of cases being of B-cell lineage [1]. Because of the fascinating interplay between Helicobacter pylori and the lymphoid system in the development of gastric marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma), this type of lymphoma has become a focus of interest in recent years [2–4].

In addition to MALT lymphoma, however, more aggressive lymphomas are also diagnosed in the stomach, with the majority being classified as diffuse large B-cell lymphoma (DLBCL). Transformation from indolent MALT lymphoma to DLBCL has repeatedly been described in the course of the disease. This is heralded by the emergence of increased numbers of transformed blast cells that eventually form sheets or clusters and finally grow to confluence, effacing any trace of the preceding indolent tumour [5,6]. In the past, resistance to H. pylori eradication has been thought to be a sign of underlying transformation to DLBCL [7]. While some investigators have raised arguments for a de novo origin of gastric DLBCL [8,9] certain features suggest that DLBCLs of the stomach are mostly transformed MALT lymphomas, as are, probably, some cases of other extranodal DLBCL [10]. In analogy to classical MALT lymphoma, more recent data have shown regression of gastric DLBCL following H. pylori eradication [11,12]. These results, nevertheless, have to be regarded as preliminary for the time being, and H. pylori eradication as sole management of DLBCL should not be applied outside the framework of a clinical study.

Recent years have seen a switch from surgery as a mainstay of treatment for gastric DLBCL [13,14] to organ conserving strategies for the management of potentially resectable
lymphomas [15,16]. Initial prospective data from our institution have demonstrated chemotherapy using the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) to be highly effective, with only moderate side-effects, for management of localised DLBCL of the stomach [15,16]. More recently, Koch et al. [17] and Binn et al. [18] have analysed the outcome of patients with gastric DLBCL undergoing chemotherapy with or without surgery, and reported equal efficacy for both approaches. While no large randomised trials on this topic have been performed, response rates and 5-year survival in the range of 90–95% have consistently been reported irrespective of treatment modality, i.e. therapy of combined modality including chemotherapy, surgery and/or radiation [17,18].

Rituximab, a chimeric monoclonal antibody targeting the CD20 epitope present on virtually all B cells, has demonstrated activity in various types of lymphoma [19,20] and has also been given to patients with MALT lymphoma [21,22]. Highly promising results have been obtained in combination with chemotherapy, and a randomised study comparing rituximab plus CHOP (R-CHOP) with CHOP alone in patients with nodal DLBCL has shown superior response rates and survival for the R-CHOP regimen [23]. According to these data, R-CHOP has increasingly been applied as primary treatment to patients with localised gastric DLBCL at our institution. As no data on the efficacy of R-CHOP in this cohort of patients have been published so far, we present our experience with the R-CHOP regimen for primary management of localised gastric DLBCL.

Patients and methods

Patients with a diagnosis of DLBCL of the stomach (with or without a MALT component) undergoing treatment with R-CHOP were analysed. Patients who had undergone prior surgery for gastric lymphoma were excluded from this series. In patients without a MALT component, absence of disease dissemination beyond abdominal lymph nodes as judged by clinical staging served as an indication of a gastric origin of the lymphoma. Histologically, DLBCL was defined according to the criteria outlined in the recent WHO classification [24]. All histological samples were evaluated by a reference pathologist (A.C.), and immunohistochemistry for CD79a and CD20, along with staining with the Ki-67 (MIB-1) antibody for assessment of cellular proliferation, was carried out in all patients.

Stage at presentation was assessed according to the Ann Arbor classification as modified by Musshoff [25] and Radaskiewicz et al. [26].

All patients with evidence of *H. pylori*-associated gastritis or a MALT component received antibiotic treatment consisting of metronidazole, clarithromycin and a proton pump inhibitor (PPI). Treatment with a PPI was continued for the whole duration of chemotherapy in order to minimise the risk of hemorrhage. As patients were scheduled for treatment on an outpatient basis, rituximab was given at the standard dose of 375 mg/m² on day 1, while chemotherapy with the CHOP regimen was given on day 2. Rituximab was started with an infusion rate of 50 mg/h and was increased every 30 min by 50 mg/h until the maximum infusion rate of 400 mg/h was reached, according to the manufacturer’s guidelines. According to our previous experience [15,16], chemotherapy was administered according to age in our patients. In patients <75 years old, standard CHOP consisting of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m² and vincristine 1.4 mg/m² (for a maximum single dose of 2 mg) was given intravenously on day 1, along with 100 mg oral prednisone on days 1–5 (CHOP). Patients >75 years old received therapy at a reduced dose: cyclophosphamide 750 mg, doxorubicin 50 mg and vincristine 1 mg total dose intravenously on day 1, and prednisone 100 mg orally on days 1–5. Premedication consisted of oral paracetamol and intravenous diphenhydramin before rituximab in all patients, and antiemetic prophylaxis with 5-HT3 receptor antagonists was administered on a routine basis before chemotherapy. For initiation of chemotherapy, a left-ventricular ejection fraction >50% as judged by echocardiography, a leukocyte count >3500/μl and a thrombocyte count >100 000/μl, as well as normal liver and renal function parameters, were required.

Cycles were repeated every 3 weeks, with re-evaluation of treatment response by means of gastroscopy with biopsies, endosonography and computed tomography (CT) scanning of thorax and abdomen every three cycles. Response to treatment was classified according to WHO standard criteria. In case of stable disease (SD), partial remission (PR) or complete remission (CR) of the lymphoma upon re-evaluation, treatment was continued for another three cycles up to a maximum of six cycles. In case of lymphoma persistence after completion of chemotherapy, consecutive local irradiation was performed after chemotherapy.

Follow-up procedures included gastroscopy with biopsies and endosonography, and CT scans every 3 months during the first 2 years, with 6-month intervals between re-evaluations thereafter.

Results

Our study identified 15 patients (eight females, seven males) aged between 59 and 88 years who were given R-CHOP for treatment of early-stage gastric DLBCL (Table 1), reflecting the demographics of patients with gastric DLBCL at our institution during the respective time span. All patients were chemotherapy-naïve and none had undergone prior surgery. Nine patients had evidence of *H. pylori* infection at diagnosis and received concomitant antibiotic therapy, and only two patients also had a MALT component suggestive of transformation into DLBCL from underlying MALT lymphoma.

A total of 79 cycles were administered to our patients, with a median of six cycles per patient (range three to six). Taken together, 13 patients (87%) achieved a CR and two (13%) had a PR. As also seen in previous series [15,16], 11 of 13 patients reached CR at the first re-assessment, i.e. after three cycles of treatment. Owing to documented CR after first re-assessment, one patient discontinued treatment for personal reasons after three courses of R-CHOP and remains alive without evidence of disease 33 months after initiation of treatment.

After a median follow-up of 15 months (range 4–42) after treatment, three patients have died. One died from cause unrelated to lymphoma while in continuous CR 36 months after the start of chemotherapy, and there were two deaths from lymphoma progression; the other patients are alive and in durable CR. One of the patients who died due to lymphoma progression had a PR after six cycles and reached CR after additional radiation therapy. A multifocal, intraabdominal relapse located just outside the original radiation field occurred 8 months after completion of therapy and the patient died during second-line radiation therapy. The other patient...
who died from lymphoma progression achieved a PR after six cycles of R-CHOP and was also referred for radiotherapy. However, progressive disease was documented immediately after radiation therapy and the patient died despite initiation of chemotherapy with ifosfamide, carboplatin and etoposide. So far, no relapse has occurred in patients who achieved a CR after chemotherapy. As expected, side-effects of the R-CHOP regimen were moderate and mainly haematological. The predominant toxicity was leukocytopenia WHO grade 3 and 4 in 10 and five patients, respectively. Febrile leukopenia occurred in three patients, and one of them developed perianal subcutaneous infection necessitating surgical incision and consecutive antibiotic therapy. Four patients had anorexia WHO grade 1 and one patient had nausea/emesis WHO grade 2. Two patients suffered from stomach pain during therapy despite the use of a PPI, but no gastrointestinal bleeding or gastric perforation were noted. Total alopecia was seen in all of our patients. Reactions to application of rituximab were only mild with the standard premedication. The majority of patients experienced a transient fever and chills/rigors during the first rituximab infusion, which were managed by short discontinuation with consecutive slowing of the infusion rate, and one patient had an allergic skin rash during the first infusion with rituximab. No recurrence of these symptoms was noted during the following infusions.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Stage</th>
<th>IPI</th>
<th>MALT</th>
<th>Additional therapy</th>
<th>Response</th>
<th>Follow-up (months)</th>
<th>Survival</th>
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<td>0</td>
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<td>88</td>
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<td>3</td>
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<td>CR</td>
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<td>II1</td>
<td>1</td>
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<td>CR</td>
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<tr>
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<td>CR</td>
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IPI, International Prognostic Index; MALT, MALT lymphoma plus diffuse large B-cell lymphoma; F, female; M, male; CR, complete remission; PR, partial remission; II1, involvement of regional lymph nodes; II2, involvement of distant lymph nodes; *ICE*, ifosfamide, carboplatin and etoposide.

There is ample evidence to support the concept of gastric conservation by applying systemic chemotherapy [17,27–29], and it has repeatedly been shown that resection prior to chemotherapy did not influence the CR rate, survival or disease-free survival in patients with gastric DLBCL [17,18,27–32]. To the current knowledge, patients with an underlying MALT component do not appear to be pronostically different, and thus do not require a different approach, as *H. pylori* eradication has been shown to be effective in both subtypes of gastric lymphomas.

Our data demonstrate that R-CHOP is safe and highly effective for the management of localised gastric DLBCL. The rationale for administering R-CHOP to such patients was based on findings obtained in patients >60 years old suffering from nodal DLBCL, in whom superior response rates and survival for the R-CHOP regimen were found compared with CHOP alone [23]. All patients given R-CHOP at our institution responded to treatment, with 13 of 15 having CR (87%) while two had a PR (13%). However, both patients who achieved only a PR died from lymphoma 10 and 17 months after initiation of therapy despite additional radiotherapy. The high response rate and the fact that the large majority of patients (11 of 13) reached CR after three courses of therapy again confirms the fact that gastric DLBCL is a highly chemosensitive disease. In spite of the fast response, no problems in terms of bleeding or perforation were encountered in our patients, who were all given concomitant therapy with oral PPIs on a routine basis. Dose reduction of CHOP to 1 m² in patients >75 years old did not diminish therapeutic efficacy in our patients. Therefore, one might speculate that a large proportion of patients could be overtreated with application of six full courses of chemotherapy, as also stated in a previous report [16]. As this hypothesis is
based on retrospective evaluation of results, a formal prospective trial would be warranted to definitely answer this question.

The good results with the R-CHOP regimen are not unexpected, given the good prognostic parameters of our patients in terms of stage and International Prognostic Index (IPI) (see Table 1), and also in view of the excellent data reported for application of conventional CHOP chemotherapy in patients with gastric DLBCL. In fact, recently published results obtained in patients with gastric DLBCL beg the question of whether uncritical extrapolation from nodal DLBCL is justified. Initial prospective data from our institution have demonstrated chemotherapy using the CHOP regimen to be highly effective, with only moderate side-effects, for the management of localised DLBCL of the stomach [15,16]. All patients treated with CHOP achieved a CR, and no relapses were seen after a median follow-up of 39 months. However, a recent French analysis retrospectively comparing anthracycline-containing chemotherapy with or without gastric resection disclosed similar good results, with 5-year survival and event-free survival rates of 90% in patients with IPI 0–1 [18]. Whether the addition of rituximab to the conventional CHOP regimen really offers a clinical advantage remains to be elucidated in randomised trials, as the data presented in our analysis do not allow an answer to this question. However, in view of the excellent results with CHOP, such a study would have to be very large and have a long follow-up period in order to detect a statistical significance both for response and survival. In the absence of such data, and considering the costs added by rituximab, it is probably premature to suggest R-CHOP as standard treatment outside of a clinical trial in view of the excellent results with CHOP, such a study would have to be very large and have a long follow-up period in order to detect a statistical significance both for response and survival. In the absence of such data, and considering the costs added by rituximab, it is probably premature to suggest R-CHOP as standard treatment outside of a clinical trial in patients with localised gastric DLBCL, as their outcome appears to be excellent with standard CHOP treatment.

References


