Chemotherapy for management of localised high-grade gastric B-cell lymphoma: how much is necessary?

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Background: Recent data suggest that chemotherapy with the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen is a highly effective treatment for localised primary gastric lymphoma of diffuse large B-cell histology (DLBCL). We have reported that the large majority of patients achieve complete remission (CR) following three cycles of treatment, and now provide an updated series with special emphasis on patients receiving only short-term chemotherapy.

Patients and methods: All patients with a histologically verified diagnosis of gastric DLBCL in stages EI and EII1 undergoing chemotherapy with the CHOP regimen were evaluated. Data analysed included clinical stage, histology [presence of an additional mucosa-associated lymphoid tissue (MALT) component], evidence of Helicobacter pylori infection, H. pylori eradication, time to CR, survival and regular restaging (i.e. after three and six cycles, respectively).

Results: A total of 37 patients with DLBCL of the stomach with localised disease were identified, five of whom also had a MALT component. Twenty-two patients presented with stage EI and 15 with stage EII1 disease. All patients were given chemotherapy as sole management of their lymphoma; 36 patients received CHOP, while one patient was given CHOP along with rituximab. Thirty-two (86%) achieved a CR after a maximum of three cycles, while only four patients had to be given six cycles for CR. In total, nine of 37 patients (24%) discontinued therapy earlier than scheduled: one patient received one cycle, two received two, six received three and one patient received four cycles. Two of these patients stopped treatment due to toxicity, i.e. protracted thrombocytopenia or chemotherapy extravasation. One additional patient died after one cycle of treatment; autopsy disclosed no signs of remaining lymphoma. Three patients have died after a median follow-up of 39 months (including the one patient who discontinued therapy after one cycle of treatment), while the remaining 34 patients are alive without evidence of disease. Twenty-four out of 37 patients (65%) had also undergone H. pylori eradication (including six of nine patients receiving only short-term treatment).

Conclusions: DLBCL of the stomach appears to be a highly chemosensitive disease. Our data question the need for full-term CHOP treatment in patients achieving CR upon first follow-up. However, recent data suggest that additional H. pylori eradication might have contributed to the excellent results achieved in our series.

Key words: CHOP, diffuse large B-cell lymphoma, stomach

Introduction

The stomach is the most common site of extranodal lymphoma. The large majority of cases are of B-cell lineage, while primary gastric T-cell lymphomas are exceedingly rare [1]. The discovery of a causal role for Helicobacter pylori in the development of gastric marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT)-type has drastically altered the therapeutic approach to patients with early stage disease [2–4]. According to recent data, durable complete remissions (CRs) may be achieved in up to 80% of patients with early stage MALT-type lymphoma following eradication of the bacteria [4].

In addition to the ‘classical’ indolent MALT-type lymphoma, aggressive histologies are also encountered in the stomach, the majority being classified as diffuse large B-cell...
lymphoma (DLBCL). Transformation from indolent MALT-type lymphoma to a more aggressive type ('high-grade lymphoma') has repeatedly been described in the course of the disease. This is heralded by the emergence of increased numbers of blast cells, which eventually form sheets or clusters [5, 6] and finally grow to confluence, effacing any trace of the preceding indolent tumour. While some investigators have raised arguments for a de novo origin of gastric DLBCL [7, 8], certain features suggest that these tumours are mostly derived from MALT-type lymphomas, as are probably some cases of other extranodal DLBCL [9]. These include the association of such lymphomas with H. pylori infection, the absence of bcl-2 protein expression [10], which is present in 30% of high-grade nodal B-cell lymphomas, and the absence of any effect of a minor low-grade component on the clinical behaviour in some studies. In addition, 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.

While surgery (with or without additional application of chemotherapy) has been the preferred form of treatment in the past for gastric DLBCL [13, 14], organ-conserving strategies are increasingly being applied. In a prospective study including 25 patients with gastric DLBCL in localised stages, we have found chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) to be highly effective, with only moderate side effects [15]. Of interest is the fact that 21 of 24 patients evaluable for response achieved CR after three courses of CHOP, and the remaining three patients after six cycles. At the time of our initial analysis, seven of 25 patients had been given only between one and four cycles of therapy, and had permanently stopped therapy either due to personal reasons (six patients) or prolonged thrombocytopenia (one patient). Upon our initial publication, all of these patients with the exception of one, who died 15 months after her first (and only) cycle of treatment, were alive after a follow-up of between 16 and 44 months. These findings suggest that primary gastric DLBCL is a highly chemosensitive disease and potentially question the need for prolonged chemotherapy as usually applied for nodal DLBCL.

In this article, we provide an extended follow-up of all our patients with localised DLBCL of the stomach undergoing CHOP chemotherapy, with emphasis on time to CR and survival after short-term chemotherapy. This is an extension of our previous series, now including an additional 12 patients with similar characteristics and a prolonged follow-up time.

Patients and methods

All patients with a diagnosis of localised high-grade B-cell lymphoma of the stomach (with or without a MALT component) admitted at the University of Vienna and the Department of Internal Medicine, Hospital Ramon y Cajal, Madrid, for application of chemotherapy were analysed. Patients with prior surgery for gastric lymphoma were excluded from this series. Primary gastric high-grade B-cell lymphoma was defined as high-grade lymphoma arising in a background of extranodal marginal zone B-cell lymphoma of MALT type. In patients without a MALT component, absence of disease dissemination beyond local nodes as judged by clinical staging (vide infra) served as an indication of a gastric origin of the lymphoma. Histologically, primary gastric high-grade B-cell lymphoma represents diffuse large B-cell lymphoma of the revised European–American classification of lymphoid neoplasms [16]. As such it is mostly composed of large cells resembling centroblasts or large non-cleaved cells. Histologic analysis of patients presented in this series was performed by a reference haematopathologist (A.C.).

Stage at presentation was assessed according to the Ann Arbor classification, modified by Musshof, and the extent of staging was also analysed.

Results

A total of 37 patients—25 of whom had been included in an earlier report [15]—with a diagnosis of gastric DLBCL in stages E1 and E1, were identified (22 in stage E1 and 15 in stage E1), while five had an additional MALT component. Patients age ranged from 32 to 93 years, with nine patients >75 years of age.

Chemotherapy was administered according to the age of the patients. In patients <75 years of age, treatment consisted of cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2 and vincristine 1.4 mg/m2 (for a maximum single dose of 2 mg), all given intravenously (i.v.) on day 1, along with oral prednisone 100 mg on days 1–5 (CHOP). Patients >75 years of age received therapy at a reduced dose: cyclophosphamide 750 mg, doxorubicin 50 mg and vincristine 1 mg total dose i.v. on day 1, and prednisone 100 mg p.o. on days 1–5. Antiemetic prophylaxis with 5-HT3-receptor antagonists was administered on a routine basis; no uroprotection was given other than standard hydration. For initiation of chemotherapy, a left-ventricular ejection fraction >50% as judged by echocardiography, a leucocyte count >3500/µl and a thrombocyte count >100000/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 chest and abdomen every three cycles. Response to treatment was classified according to World Health Organization (WHO) standard criteria. In the case of stable disease, partial regression or CR of the lymphoma upon re-evaluation, treatment was continued for another three cycles up to a maximum of nine cycles, or six cycles in the cohort of older patients.

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. Colonoscopy, contrast X-ray of the small bowel, otolaryngological and ophthalmological evaluations were performed every 12 months in order to exclude the presence of lymphoma relapse in distant mucosal sites. All patients under-
went gastroscopy with multiple biopsies, CT scanning of thorax and abdomen, and a bone marrow biopsy for initial staging, while in 33 patients initial extensive staging including endosonography, contrast X-ray of the small bowel and a colonoscopy. However, all patients except two were referred for at least one endosonographical assessment in the course of therapy. Twenty-one of these 33 patients also underwent otorhinolaryngological assessment including sonography or magnetic resonance imaging of the salivary glands and lacrimal glands.

All patients with evidence of *H. pylori*-associated gastritis, positive serology or a MALT-component received antibiotic treatment consisting of metronidazole, clarithromycin and a proton pump inhibitor (PPI). Accordingly, application of antibiotics for the eradication of *H. pylori* was documented in 24 of our patients. Treatment with a PPI was continued for the whole duration of chemotherapy in order to minimise the risk of haemorrhage.

Thirty-six patients were considered evaluable for response, while one patient, 83 years of age, refused further therapy due to pronounced improvement of her condition after the first cycle of therapy, and she died 15 months later from gastric haemorrhage. All 36 patients considered evaluable for response achieved a CR, 30 after three courses, one patient each after two and after four courses, and the remaining four after six cycles of CHOP. One patient died shortly after the first course of therapy due to gastric perforation after refusal of therapy with a PPI. Upon autopsy, however, no evidence of lymphoma could be documented, and the patient was rated as CR. Apart from this, no treatment-related mortality was recorded.

Thirty-two patients were alive after a median follow-up of 39 months (range 0.5–87 months), two were lost to follow-up (after 18 and 87 months, respectively) and three patients had died (one from treatment-related toxicity, one from a stroke having been in CR for 8 months and one patient from gastric bleeding, probably related to progression of the lymphoma, 15 months after refusing continuation of therapy after the first cycle).

A total of nine patients (not including the patient who died from perforation after the first cycle) discontinued treatment prematurely: one patient each after one and after two courses, six patients after three cycles and one patient after four cycles. Toxicities, i.e. protracted thrombocytopenia and skin necrosis due to chemotherapy extravasation requiring subsequent plastic surgery, were the reason for discontinuation in two patients. In the other cases, chemotherapy was stopped at the patients’ request despite the absence of toxicity exceeding WHO grade 2.

One patient had died from gastric bleeding 15 months after receiving only one cycle of treatment, and one patient, 93 years of age, was lost to follow-up 18 months after obtaining CR following three cycles of CHOP. The other seven patients are alive without evidence of disease between 12 and 56 months after initiation of therapy (Table 1). Six of these nine patients had also undergone successful *H. pylori* eradication, while two of the four individuals requiring six cycles to obtain a CR had been given antibiotics due to evidence of *H. pylori* infection.

**Discussion**

Recent years have seen a profound change in the management of gastric lymphoma, especially in patients suffering from extranodal marginal zone B-cell lymphoma of the MALT-type [2, 17]. As opposed to previous approaches, organ-conserving strategies including *H. pylori* eradication or radiotherapy are being applied, resulting in survival rates comparable to surgical intervention. Chemotherapy, however, has not been adequately tested so far in patients with localised gastric MALT-type lymphoma [13, 15–17].

In contrast to this, cytotoxic drugs are more commonly applied as a part of therapeutic strategies for DLBCL, albeit mostly following surgery or in patients with advanced disease deemed unresectable. In a series including 185 patients,

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<th>Table 1. Characteristics of patients undergoing short-term chemotherapy</th>
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F. female; M. male; DLBCL, lymphoma of diffuse large B-cell histology; HP, *Helicobacter pylori*; MALT, mucosa-associated lymphoid tissue.
Ibrahim et al. [18] found that surgery had been part of the therapy in 104 patients, while a total of 72 patients (including 33 patients with stage IV disease) had undergone chemotherapy only. In addition, some of these patients did not receive anthracyclines as part of the therapeutic regimen. This is also mirrored by similar data reported by Cortelazzo et al. [19], who analysed 312 patients with localised gastric DLBCL treated in eight Italian and one Swiss centre. In total, 239 patients underwent gastric surgery followed by chemotherapy in 147, by chemotherapy plus radiation in 39 and by radiotherapy in seven cases, while only 54 patients were given chemotherapy as sole management.

Prospective data on the use of chemotherapy alone in stage EII and EII1, however, are still scarce. While Koch et al. [20] have demonstrated equal efficacy with conservative management as compared with surgery in localised gastric lymphoma, this series also included radiation to the stomach as local therapy. H. pylori eradication was not routinely applied due to the start of the study being prior to when H. pylori eradication was routine. In a series performed at our institution, we have demonstrated excellent efficacy for conventional CHOP chemotherapy in 25 patients with localised DLBCL, with all patients evaluable for response achieving CR. In this report, we have noted that time to remission was 3 months in 21 of 25 patients, and that neither reduction of dose in elderly patients nor early discontinuation of therapy appeared to impair the activity of chemotherapy.

The current analysis provides an extended follow-up and now includes 37 patients as opposed to our initial study with only 25 patients [15]. Our data add further support to the notion that localised gastric DLBCL is a highly chemosensitive disease. Thirty-two of 36 patients judged evaluable (89%) achieved CR after a maximum of four cycles of therapy, and only three patients had died after a median follow-up of 39 months. In addition, no local recurrences have occurred in our patients. As retrospective studies have shown that the risk for relapse with DLCBL rapidly declines 24 months after initial therapy [21], these CRs might translate into long-term CR or even cure of our patients. Meticulous follow-up, however, still appears to be indicated, as late relapses with MALT-type lymphoma have been reported also following successful therapy of initial (probably transformed) DLBCL.

Especially interesting is the fact that nine patients discontinued therapy earlier than scheduled. This rate of lack of compliance with scheduled treatment is relatively high, but is probably related to the fact that the first reassessment of disease status was performed after just three courses of treatment. As a high proportion of patients were already in CR after this restaging, this information might have adversely influenced patients against further prolongation of therapy. One of these patients, a patient aged 83 years, died 15 months after application of only one course of therapy, while another, aged 93 years, was lost to follow-up after 18 months in CR (Table 1). The other patients are alive without evidence of disease between 12 and 56 months after initiation of therapy. Six out of these nine patients also underwent H. pylori eradication before application of CHOP therapy, while the total number of patients being treated with antibiotics was 24. Given recent data published by Morgner et al. [11] and Montalban et al. [12], who have documented prolonged CR in patients with gastric DLBCL following H. pylori eradication alone, we cannot rule out the fact that H. pylori eradication given along with chemotherapy might have contributed to the excellent results seen in our patients. In view of this, however, it appears reasonable to recommend (additional) H. pylori eradication in all patients with gastric DLBCL in case of direct or indirect evidence of H. pylori infection.

Taken together, our data indicate that a subset of patients with primary gastric DLBCL achieving CR after H. pylori eradication and three cycles of CHOP might be overtreated with prolonged chemotherapy or combined radiochemotherapy. While it is too early to recommend short-term chemotherapy only for management of localised gastric DLBCL outside a clinical trial, we think that these data warrant further investigation in order to define the optimal approach to this disease.

References