Complete long-term response to radiotherapy of gastric early-stage marginal zone lymphoma resistant to both anti-*Helicobacter pylori* antibiotics and chemotherapy

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**Background:** The optimal approach to patients with gastric lymphoma of extranodal mucosa-associated lymphoid tissue (MALT) that resist to anti-*Helicobacter pylori* (HP) eradication therapy is still to be defined.

**Patients and methods:** From January 1997 to December 2004, we observed 24 patients affected with newly diagnosed early-stage and HP-positive gastric lymphoma of the MALT type. Five of them resisted to oral anti-HP antibiotic regimens and to subsequent one (two patients) or two (three patients) chemotherapy regimens. Age ranged between 51 and 77 years (median 70); three were females. Translocation (11;18) was ascertained in one subject. They were admitted to local radiation therapy with a total dose of 30 Gy.

**Results:** All such resistant patients achieved complete remission after radiotherapy. No relapses were observed after 21, 45, 48, 52, and 67 months of uninterrupted follow-up. Early toxicity was very low and consisted of mild nausea. Late toxicity or secondary malignancy was not recorded so far.

**Conclusions:** Radiotherapy proved to be effective and safe for early-stage HP-positive gastric extranodal lymphoma of MALT type that is resistant to anti-HP eradication antibiotics and to following chemotherapy. Radiotherapy might be suggested as principal salvage therapy after resistance to HP eradication, instead of chemotherapy.

**Key words:** chemotherapy, gastric MALT lymphoma, *Helicobacter pylori*, radiotherapy

**introduction**

The stomach is the relatively most common origin of the mucosa-associated lymphoid tissue (MALT) lymphoma, now termed as extranodal marginal zone B-cell lymphoma of MALT type [1]. It has become a focus of interest due to its pathophysiological link with *Helicobacter pylori* (HP) and the consecutive high rate of response to HP eradication therapy [2]. In view of this, anti-HP antibiotic therapy has become the standard treatment for patients with localized disease, and recent data—contrary to previous reports [3]—have suggested that even HP-negative patients might benefit from antibiotics [4]. In case of nonresponse, however, the standard approach is unclear. Both surgery, chemotherapy, and radiation therapy have shown promising results as front-line treatments, and at present there is only one randomized study [5], which nevertheless suggests chemotherapy as the management of choice. Very larger cooperation and long-term accruals should be required by a randomized trial which would investigate the best therapy for HP-resistant or HP-negative patients since these cases are no more than 10%–20% of all early-stage patients with gastric lymphoma of the MALT type, and this represents only 2%–3% of all non-Hodgkin lymphomas.

However, some clues on the superiority of one therapy can be drawn even from small cohort of patients through the analysis of the responses recorded in subjects who have become resistant to the other prior treatments.

Here we report the excellent results of gastric irradiation in some patients whose gastric MALT lymphoma failed to respond to HP eradication and subsequent chemotherapy.

**patients and methods**

From January 1997 to December 2004, 24 patients affected with newly diagnosed early-stage, HP-positive gastric lymphoma of the MALT type were referred to our Units. All were histologically reevaluated for both the correct diagnosis of marginal zone B-cell lymphoma and the presence of HP in their gastric specimens. Serology for HP and urea breath testing were not routinely used.

Staging procedures included computed tomography of thorax abdomen and pelvis, bone marrow biopsy and aspirate, abdomen ultrasonography, complete blood count, and biochemical profile of the serum. Eleven subjects had baseline endoscopic ultrasonography. According to the
so-called Lugano Classification [6], 18 presented stage IE disease and six had stage IIIE disease. All underwent an oral treatment protocol for HP eradication which consisted of amoxicillin 1000 mg, clarithromycin 500 mg, and omeprazole 20 mg, b.i.d. for 7 days. Endoscopic evaluation of response, with systematic biotical mapping, was carried out at 3 and 6 months and then at 6-month interval for 2 years, then yearly thereafter. Response to therapy was evaluated with reference to the histological scoring system of Wotherspoon et al. [7]. Complete remission was defined as the absence of any lesion or the presence of lesions corresponding to a score not greater than 2 in any biotical specimen; partial remission was considered the persistence of histological lesions with Wotherspoon’s score 3 and no lesions with scores 4 or 5 on any histological section (this last condition actually corresponding to response failure). The judgment of complete remission had to receive at least one confirmation at the subsequent endoscopic examination.

Patients with persisting presence of HP and null response of the lymphoma at 6 months or partial response at 12 months from the first eradication therapy were offered the possibility of second-line regimen according to general clinical considerations, patient’s preference, or clinician’s discretion. This alternative regimen included tetracycline 500 mg, metronidazole 500 mg, and omeprazole 20 mg, b.i.d., orally.

Chemotherapy

Patients with incomplete response of the lymphoma either after two HP eradication therapies or without presence of HP after one antibiotic were admitted to chemotherapy. The allowed regimens were the following: (i) CP [8], chlorambucil 15 mg/sqm plus prednison 60 mg/sqm, orally, days 1–5 every 28 days for six cycles; (ii) COP [9], cyclophosphamide 600 mg/sqm i.v., day 1, vincristine 2 mg i.v., day 1, prednison 60 mg/sqm p.o., days 1–5, every 21 days for six cycles; (iii) CHOP [10], cyclophosphamide 750 mg/sqm i.v., day 1, doxorubicin 50 mg/sqm i.v., day 1, vincristine 1.4 mg i.v., day 1, prednison 100 mg p.o., days 1–5, every 21 days for six cycles. Rituximab was not used, doxorubicin 50 mg/sqm i.v., day 1.

Patients resistant to chemotherapy, i.e. with persistence of lymphomatous lesions corresponding to Wotherspoon’s score 4 or 5, were admitted to radiotherapy.

Radiotherapy

The radiation was limited to the involved field which included the whole stomach (clinical target volume) plus 2.5 cm of surrounding margins to account for setup and internal margin errors (planned target volume) using a 3D conformal radiation technique. Planning geometry consisted in three beams (0°, 90°, and 270°) using high photon energy (6 + 18 MV). Patients underwent the computed tomography (CT) scan simulation after overnight fast, in the supine position. The stomach and the organs at risk (spinal cord, kidneys, liver) were defined on the CT slices. Patients were treated in the morning, in fasting condition (i.e. with empty stomach). The radiation total dose was 30 Gy, with daily fractions of 2 Gy. Prophylactic oral medication with omeprazole 20 mg every 12 h and metoclopramide 10 mg before meals was prescribed all over the time of the treatment.

**results**

The clinical characteristics of the five patients resistant to anti-HP therapy are reported in Table 1, which also details the chemotherapy regimens administered, the responses to chemotherapy, the doses of radiotherapy, the response to radiotherapy, and the remission durations. Patient MF (see Table 1) had surgical excision of a ‘pseudo-lymphoma’ of the upper lobe of right lung 6 years before the diagnosis of gastric lymphoma: the histologic reevaluation of the pulmonary lymphoma: the histologic reevaluation of the pulmonary

<table>
<thead>
<tr>
<th>Case</th>
<th>MF</th>
<th>TL</th>
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<tbody>
<tr>
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<tr>
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<td>CHOP</td>
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<td>COP</td>
<td>COP</td>
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<tr>
<td>Second</td>
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<td>CR</td>
<td>CR</td>
<td>CR</td>
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<tr>
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<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
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<td>70</td>
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<td>52</td>
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<td>NED</td>
<td>NED</td>
<td>NED*</td>
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</table>

*Death for thrombotic stroke.

Table 1. Patient characteristics, treatments, and responses

HP, Helicobacter pylori; CT, computed tomography; RT, radiotherapy.

specimens allowed the recognition of an extranodal marginal B-cell lymphoma of the bronchus-associated lymphoid tissue. Two patients (MM (see Table 1) and SO (see Table 1)) underwent a second-line chemotherapy after the failure of the first-line regimen, according to their wills, since both preferred to delay the use radiotherapy.

A complete remission was achieved in all patients, irrespective of the ulcerative nature of the lesion persisting after chemotherapy.

Toxicity during radiotherapy was easily tolerable and consisted of anorexia and mild (Eastern Cooperative Oncology Group grades 1–2) and inconstant nausea. Slight reduction in hematologic count never required the administration of growth factors. In particular, none of the patients experienced gastric perforation or hemorrhage, renal, or hepatic toxic effects and none developed metachronous tumors in their follow-up. All patients are still living, except VV (see Table 1), aged 78 years at the diagnosis, who died of thrombotic stroke after ~4 years of uninterrupted complete remission.

**discussion**

It is difficult to reach a firm opinion on what is the best primary treatment of the gastric marginal zone B-cell lymphoma of MALT type. The rarity of the disease justifies the very small number of randomized trials carried out so far, and the good response rate attainable with various treatments (surgery, chemotherapy, radiotherapy, antibiotic therapy, anti-CD20 immunotherapy) makes comparisons complex, so that the evaluation has to rely also on complementary end points, such as time to response, probability of relapse, patient’s quality of life, survival without gastrectomy, and whole costs. Historically, very good results have been obtained with gastrectomy alone or in combination with other treatments [11]. Both chemotherapy [12] and radiotherapy [13] proved to be very effective when administered alone or in combination, with or without prior gastrectomy. Now, reports on good results with rituximab are also available [14]. Today the evidence collected on the promoter role of the HP toward the neoplastic transformation of the primarily reactive lymphocytes and the demonstration of regression of early-stage lymphoma in response to antibiotics
effective against HP have made the choice of antibiotic therapy the first approach in most cases of early-gastric lymphoma of the MALT type. However, 20%–30% of the patients lack HP in their gastric biopsies, though most of them show circulating antibodies anti-HP, and there is general consensus that antibiotic eradication is useless in these cases [15], except sporadic reports [4] still to be confirmed. Moreover, response of HP infection to antibiotics can be independent of that of the lymphoma. Anyhow, ~20%–30% of HP-positive patients do not reach complete histologic regression of their lymphoma, though prolonged endoscopic follow-up after antibiotic HP eradication [15]. With respect to this, our proportion of nonresponders to anti-HP eradication therapy is in agreement with the figures of other reports [16].

Thus, HP-negative patients and those HP positive whose lymphoma does not respond to eradicating therapy need alternative treatments. For these cases, surgery, chemotherapy, and radiotherapy have distinct pros and cons that are even more difficult to evaluate than as primary treatments.

Since gastric lymphoma of MALT type is often an actually localized disease, local treatment approaches are destined to be successful, as it was largely demonstrated by surgery and radiotherapy. Surgically treated patients can reach near 100% of 5-year survival [17] but operative mortality can be up to 5% and postgastrectomy morbidity can involve 20%–25% since often a simply partial resection of the stomach cannot be carried out due to either multifocal or fundic localization of the tumor. Some cases can be considered truly ‘gastric cripples’. So, though highly effective, gastrectomy receives a decreasing interest [18] and now is offered to resistant gastric MALT lymphoma patients with concern even as second-line approach.

The sensibility of gastric lymphomas to chemotherapy is well-known, though there is not a standard treatment [19]. Chemotherapy has advantages in cases with suspected systemic dissemination and is active in nonresponders to anti-HP eradication therapy or in relapsed subjects. Length of treatment and general toxicity are its main drawbacks.

Radiotherapy shares the strict radicality and localized activity of surgery on the one hand and the conservative advantage of chemotherapy on the other, together with its own advantage of short duration and minimal early and late toxicity at the low doses currently administered. Indeed, the main argument against irradiation of the stomach can be the risk of perforation and bleeding, renal toxicity, and second malignancies. The review of the literature has already confirmed that such risks are minimal. The risk of gastric bleeding and perforation during chemotherapy and/or radiotherapy in unresected patients is ~4%; it mainly occurs in advanced stage cases and is comparable with the perioperative risk of death related to gastrectomy itself [20]. Moreover, the diffuse development of irradiation techniques, with a CT-aided planning of the irradiated volume and the use of multileaf collimators for field shaping, minimizes the exposure of kidneys and liver to radiations. The risk of second malignancy has to be considered absolutely rare but—as a matter of fact—hardly distinguishable from that intrinsically related to HP exposure as a crucial pathogenetic step, common to lymphoma and carcinoma, and independent of subsequent agents and therapies. Our patients confirm these conclusions since they all experienced minimal nausea and anorexia during radiotherapy, though delivered after one or two chemotherapy regimens. Only after radiotherapy they achieved that complete and durable response that chemotherapy was not able to provide them. Moreover, nobody developed second malignancy in spite of the combined treatments and the long enough follow-up time. These results agree with those obtained by Sugimoto et al. [21] on their three patients, refractory to HP eradication therapy, with the only difference that they underwent radiotherapy soon after the failure of antibiotics against HP without an intermediate chemotherapeutic step. Due to their lack of response to antibiotics, it is probable that HP-resistant patients, like the four ours who did not receive cytogenetic study, actually carry the t(11;18) translocation, which is considered as distinct subgroup, resistant to eradication therapy.

Interestingly, a comparison of the estimated costs (drawn from charges of Regione Lombardia) of the second-line treatments currently used after anti-HP antibiotic failure, as can be seen in Table 2, shows that a 30-Gy course of radiotherapy of the stomach is less expensive than a surgical gastric resection and costs ~20% less than six cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy. Oral chemotherapy or cyclophosphamide, vincristine and prednisone (COP) regimen is less expensive than radiotherapy, but they do not warrant complete success in any patient. Rituximab infusion is far the most expensive treatment for gastric lymphomas even when administered alone.

In conclusion, our five cases, that can be considered as cured by radiation therapy as third-line treatment, suggest that patients resistant to HP eradication might very probably benefit by radiotherapy as direct second-line treatment with high efficacy, low side-effects, short time, and low costs, without any intermediate attempt with chemotherapy. The same indication might be valid also for patients HP negative at diagnosis for whom pioneer experiences are available [22] and those presenting t(11;18), but further studies are needed to reach a definite conclusion on this matter.

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### Table 2. Actual costs of some treatments of gastric lymphoma of MALT type resisting to anti-HP antibiotic therapy (charges of Regione Lombardia, 2008 with computation drug costs, ambulatory medical examinations, administration of a 30-Gy radiotherapy total dose with 2-Gy day fractions, gastric surgery with a 14-day hospitalization)

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Quantity</th>
<th>Administrative conditions</th>
<th>Total €</th>
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<tbody>
<tr>
<td>CP</td>
<td>6 cycles</td>
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<td>87 700</td>
</tr>
<tr>
<td>COP</td>
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<td>146 700</td>
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<tr>
<td>CHOP</td>
<td>6 cycles</td>
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<tr>
<td>Rituximab</td>
<td>6 cycles</td>
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<td>1 664 400</td>
</tr>
<tr>
<td>Radiotherapy</td>
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<tr>
<td>Gastrectomy</td>
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<td>Inpatient</td>
<td>814 700</td>
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MALT, mucosa-associated lymphoid tissue; HP, Helicobacter pylori.
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references