

STOMACH PRESERVATION IN LOW- AND HIGH-GRADE PRIMARY GASTRIC LYMPHOMAS: PRELIMINARY RESULTS

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ABSTRACT

Background. The optimal management of primary gastric lymphomas has yet to be defined. In the past surgery was advocated as the optimal first step for patients with PGL. Recently, an increasing number of studies suggest that chemotherapy is as effective as surgery.

Methods. Fourteen patients with PGL were treated with chemotherapy alone. For patients with low-grade lymphoma, chemotherapy consisted of mitoxantrone 5 mg/sqm on days 1 to 3. Treatment courses were administered every 3 weeks up to a maximum of 6 cycles. Patients with high-grade lymphoma received chemotherapy according to the CHOP schedule every 4 weeks up to a maximum of 6 cycles. Two patients with high-grade lymphoma were treated as low-grade lymphoma patients (one because of age and poor performance status, the other because she refused chemotherapy that would cause hair loss). Two patients with low-grade lymphomas who did not respond to mitoxantrone were crossed over to CHOP.

Results. All patients were evaluable for toxicity, 13 for response to therapy and survival. Toxicity was mild or moderate. Neither perforation nor hemorrhage was observed. Eleven patients achieved a complete remission (85%), 1 a partial remission (7.5%) and 1 underwent disease progression (7.5%). At a median follow-up of 12 months (range 4-44 months) all complete responders are alive and disease free.

Conclusions. Although the number of evaluable patients is too small to draw any final conclusions, chemotherapy seems to be as effective as surgery in PGL, and stomach preservation improves the quality of life of the patients.

Key words: primary gastric lymphomas, chemotherapy

Primary extranodal non-Hodgkin's lymphomas account for 10-30% of all non-Hodgkin's lymphomas. The most common site of extranodal lymphomas is the stomach where they represent less than 5% of all malignancies. While both the incidence and the mortality of gastric cancer have been decreasing over the past several years in Western countries, primary gastric lymphomas (PGL) have been steadily rising over the same period (from 3.5 to 7 per million people).¹⁻⁵

The optimal management of PGL has yet to be defined.

Up to now surgery has been regarded as

essential because it enables diagnosis and accurate staging, reduces the risk of bleeding and/or perforation after chemotherapy and/or radiotherapy, and cures some patients or has debulking value in the others.⁶⁻¹³

Of late, the need for surgery as a diagnostic tool has been decreasing because a histological diagnosis can be obtained by endoscopic biopsies in more than 90% of cases.^{1,14,15}

Staging performed with non-invasive methods is unable to distinguish between stage I and stage II1, but this distinction has no therapeutic relevance because these two stages behave similarly.^{14,16}

Endoscopic ultrasonography is able to predict correctly the depth of intramural tumor infiltration and identify patients at high risk of bleeding and perforation who should be treated surgically. Furthermore, the risk of bleeding and perforation during chemotherapy or radiotherapy has generally been overestimated.^{1,14,16}

The last indication for surgery is its therapeutic role. Most investigators still consider gastrectomy to be the primary step in the treatment strategy.⁶⁻¹³ Surgery can be considered an adequate treatment for patients with low-grade disease not infiltrating beyond the submucosa. In patients with more advanced disease, however, combined modality treatment is necessary.^{1,6,17-19} The favorable impact of surgical debulking in the outcome of PGL is questionable.^{14,16,20} Finally, surgery is not feasible in one third of the cases due to tumor extension or the patient's clinical condition,¹⁴ and it carries morbidity and mortality rates which must not be underestimated.¹⁶

An increasing number of studies have begun to suggest that chemotherapy and/or radiotherapy are as effective as surgery in PGL.^{4,18,21-24} In view of these data, 14 patients with PGL were treated in a phase II study with chemotherapy alone, avoiding partial or complete gastric resection.

Patients and methods

From December 1990 to March 1995, 32 patients examined at the Oncology Department of Mantua were diagnosed as having an extranodal non-Hodgkin's lymphoma and 19 (59%) a PGL. Five of these patients were not included in this study because they underwent gastrectomy elsewhere.

Gastric involvement was established by endoscopic biopsy in 12 patients and by laparotomy in 2, because endoscopic biopsies proved to be nondiagnostic. The biopsy material was typed according to the classification of Isaacson *et al.*²⁵ The patients were staged by physical examination, inspection of Waldeyer's ring, laboratory studies including hematological values and blood chemistry, chest X-ray, ultrasonography of the upper abdomen, computed tomography

scan of the chest and abdomen, bone marrow biopsy. Endoscopic ultrasonography was performed in 3 patients. An adaptation of the Ann Arbor system for extranodal lymphomas²⁶ and its modification by Musshoff²⁷ were used for staging.

The treatment plan consisted of chemotherapy alone with two different regimens. For patients with low-grade lymphoma, chemotherapy was carried out with mitoxantrone 5 mg/sqm on days 1 to 3. Treatment courses were administered every 3 weeks up to a maximum of 6 cycles.

Patients with high-grade lymphoma received cyclophosphamide 750 mg/sqm on day 1, doxorubicin 50 mg/sqm on day 1, vincristine 1.4 mg/sqm on day 1, prednisone 100 mg on days 1 to 5 (CHOP schedule). Chemotherapy cycles were repeated every 4 weeks and a total of 6 cycles were planned. Two patients with high-grade lymphoma were treated as low-grade lymphoma patients, one because of age and poor performance status, the other because she refused therapy that would cause hair loss. Two patients with low-grade lymphoma who did not respond to mitoxantrone were crossed over to CHOP. Evaluation, including endoscopy, was performed after three cycles and at the end of treatment. Tumor responses were assessed according to the WHO classification.

Results

Initial patient characteristics are shown in Table 1. The first 14 PGL patients treated in this phase II study consisted of 9 men and 5 women with a median age of 59 (range 34-82 years). Symptoms were rather non-specific, such as epigastric pain, nausea and weight loss; hemorrhage was present in one patient, anemia in two, but without apparent bleeding. The duration of symptoms was usually long. The body of the stomach was the most common site of disease (50% of cases). Ulceration was the most frequent endoscopic pattern (57% of cases).

An appropriate diagnosis was made in 70% of cases at first endoscopic biopsy, and in 16% at subsequent biopsies; in only 14% of the cases, PGL was diagnosed surgically. Six patients were

Table 1. Initial patient characteristics.

<i>Total number</i>	14	<i>Tumor site</i>	
<i>Sex</i>		body of stomach	7
male	9	multiple anatomic region	4
female	5	gastric antrum	1
<i>Age</i>		<i>Gross features</i>	
median	59	ulceration	7
range	34-82	single	4
<i>Symptoms</i>		multiple	3
epigastric pain	8	polypoid	1
nausea	4	polypoid+ulceration	1
anemia	2	diffuse infiltration	1
weight loss	1	not classified	4
hemorrhage	1	<i>Tumor size (ulceration)</i>	
		< 5 cm	4
		> 5 cm	4
<i>Stage</i>		<i>Diagnosis on</i>	
Clinical	12	first biopsy	10
I	9	repeated biopsy	2
II1	3	laparotomy	2
II2	0	<i>Histology</i>	
Pathological	2	low grade, MALT type	6
I	0	high grade	8
II1	2	MALT type	1
II2	0	not MALT type	7

classified as having low-grade and 8 high-grade lymphomas. MALT (mucosa-associated lymphoid tissue) lymphoma was present in half of the cases. All patients were found to have limit-

ed disease (stage I or II). Twelve were staged with non-invasive methods: 9 stage I and 3 stage II1 disease. Two patients were staged surgically: both stage II1 disease.

All patients were evaluable for toxicity, 13 for response to therapy and survival. One patient was too early for response evaluation. Of the 6 patients with low-grade lymphoma, 5 (83%) achieved a complete remission and 1 a partial remission. Of the 7 patients with high-grade lymphoma evaluable for response, 6 (86%) achieved a complete remission and 1 (14%) experienced disease progression. All patients with MALT lymphoma achieved a complete remission. At a median follow-up of 12 months (range 4-44 months) all complete responders were alive and disease free (Figure 1). The only patient not responding to chemotherapy died of disease progression. Toxicity was mild or moderate. Neither perforation nor hemorrhage was observed.

Discussion

The optimal management of PGL is still under discussion. In the past, surgery was widely used with diagnostic and curative intent.⁶⁻¹³ Thanks to improvements in endoscopy and non-invasive imaging techniques, the need for surgery as a diagnostic and staging tool is decreasing.

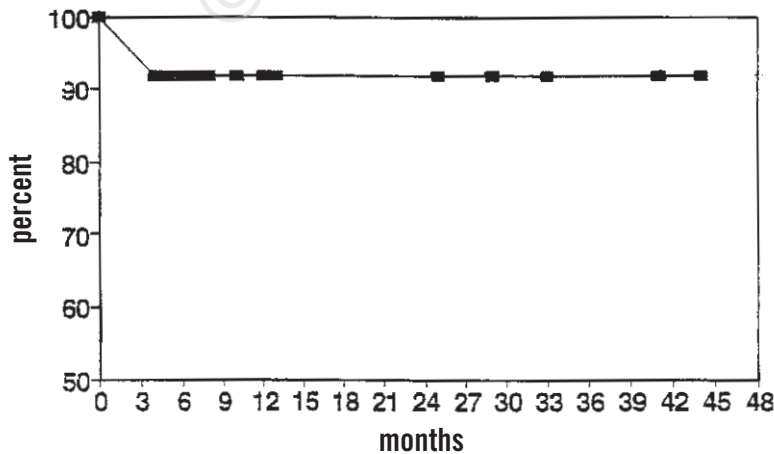


Figure 1. Survival in 13 unresected PGL patients.

In recent series, a diagnosis of PGL after endoscopic biopsies was reliable in more than 90% of all cases.^{16,29,30} According to our experience, a diagnosis of PGL was determined by endoscopic biopsy in 12 patients (86%) and by laparotomy in 2 patients (14%). Among the first group of patients, repeated endoscopic biopsies were required for diagnosis in 16% of all cases.

Only laparotomy is able to discriminate between stage I and stage III. Endoscopic ultrasonography visualizing the involvement of paragastric lymph nodes might reduce part of the understaging in non-laparotomy patients.^{6,21} Our data confirm understaging in non-laparotomy patients. Nine out of the 12 patients diagnosed by non-invasive methods (75%) were in stage I, while both patients diagnosed by laparotomy were in stage III. Furthermore, a large amount of clinical data shows that stage I and stage III behave similarly and that the distinction has no therapeutic relevance.^{6,7,10,19,31,32}

Neither hemorrhage nor perforation was observed in our patients during treatment, in agreement with more recent reviews in which the risk of bleeding and/or perforation can be estimated to be less than 5%.^{1,14,16} In any event, endoscopic ultrasonography visualizing the depth of gastric wall infiltration helps to identify patients at high risk of bleeding or perforation who should be considered for surgical treatment.¹⁴

In recent years an increasing number of studies have suggested that chemotherapy and/or radiotherapy are as effective as surgery, thus making gastrectomy unnecessary and improving the quality of life of survivors.^{14,22,23,28,33}

On the basis of these data, we started a phase II trial in which patients with PGL were treated with chemotherapy alone. Preliminary results are very encouraging. Of 13 evaluable, 11 patients achieved a complete remission (85%), 1 a partial remission (7.5%) and 1 suffered disease progression (7.5%). At a median follow-up of 12 months (range 4-44 months) all complete responders are alive and disease free. Of course, the number of evaluable patients is too small to draw any final conclusions.

The prognostic value of the histological grading of PGL is still under discussion,^{6,7,17,34} but

recent reviews reveal no significant prognostic influence for histological grading.³⁵

Nevertheless, it is important to differentiate lymphomas histologically in order to distinguish those arising in the lymph nodes from those of the MALT type.^{14,34,36} Evidence of tumor origin from MALT is associated with a relatively higher survival,^{36,37} and there is no significant difference in survival between low- and high-grade MALT lymphomas.³⁶

In our study, MALT lymphomas were present in 50% of the cases and all of them achieved a complete remission. Our MALT lymphomas were negative for *Helicobacter pylori* on endoscopic biopsies. Serum samples for the determination of *Helicobacter pylori* IgG antibodies and a breath test were not performed. Since an association was recently shown between colonization of gastric mucosa by *Helicobacter pylori*, acquisition of MALT, occurrence of low-grade MALT lymphoma and tumor regression after eradication of *Helicobacter pylori*,³⁸⁻⁴¹ we are planning to include *Helicobacter pylori* IgG antibody determination for the next patients in our trial.

In the light of this information and our preliminary results, we believe that the role of surgery as primary treatment for PGL needs to be reassessed for the following reasons:

- endoscopic biopsies can yield a positive diagnosis in the majority of patients;
- more accurate staging by laparotomy seldom changes the treatment;
- the risk of bleeding and/or perforation in unresected patients has been overestimated;
- gastric resection is associated with substantial mortality and morbidity;
- moreover, in our opinion, chemotherapy alone is as effective as surgery and stomach preservation improves the quality of life of patients.

Since individual centers generally reclude only a small number of patients over a long period, there is a need for prospective multicenter studies to ascertain the benefits and the drawbacks to every therapeutical strategy, with the aim of increasing the cure rate and reducing treatment-related complications.

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