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PRIMARY SURGERY FOLLOWED BY CHEMOTHERAPY FOR EARLY STAGE GASTRIC LYMPHOMA

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ABSTRACT

The optimal treatment of primary gastric lymphoma is controversial, surgery and chemotherapy are proposed for the treatment of primary gastric lymphoma. We evaluated the clinicopathological data and treatment results during the period 1991-1997 of thirty patients (18 males and 12 females) with a median age of 50 years (range 32-65). According to the Musshoff's staging system, the patients were classified to stage I_E (n=13), II_{1E} (n=7) and II_{2E} (n=10) and were treated with surgery (either total or subtotal gastrectomy) plus chemotherapy (CVP or CHOP). A resection with curative intent was performed in 16/20 (80%) patients with stage I_E or II_{1E}, while this rate was 4/10 (40%) for stage II_{2E} patients. Survival was significantly correlated to the type of resection (curative 80% versus non-curative 40% p<0.01). Chemotherapy was given according to the grading, CVP for 6 low-grade patients and 24 patients with intermediate and high grade received CHOP. The complete response was 93% and the five year disease free survival was 92% for Stage I_E, 86% for stage II_{1E} and 60% for stage II_{2E} (P<0.05). Surgical resection followed by chemotherapy remains the best line for primary gastric lymphoma stage I_E and II_E.

Key Words : Gastric lymphoma - Adenocarcinoma - Early stage - Surgery - clinicopathologic feature.

INTRODUCTION

Lymphoma of the gastrointestinal tract is the most common type of primary extranodal lymphomas accounting for 5 to 10% of all non-Hodgkin's lymphoma (1). Particularly primary early gastric lymphoma accounts for 29.2% of the patients who underwent surgery for gastric lymphoma and were associated with lymph node involvement in 29.9% of the patients (2). The optimal treatment for primary gastric lymphoma (PGL) is controversial. Traditionally, surgical resection of the stomach followed by chemotherapy or radiotherapy was

the therapy of choice for early stage I_E and II_E gastric lymphoma (3&4). Enthusiasm for multimodality approaches for gastric lymphoma has led to the current trend of using chemotherapy as primary treatment, thus avoiding gastric resection. Surgery, however may result in improved long term survival rates (5). However, these tumors are sensitive to chemotherapy and radiotherapy having, as reported, relatively high response rates in unresectable lesions (6). These high response rates and a better quality of life after treatment with primary chemotherapy/ radiotherapy while

preserving the stomach have recently led to an increase of conservative modalities for patients with PGL (7). Low grade gastric B-cells lymphoma of mucosa associated lymphoid tissue type (MALT) lymphoma is a recently recognized disease entity. Remarkably are the latest preliminary results for the treatment of low grade gastric MALT lymphoma when confined to the mucosa or submucosa without evidence of nodal involvement, that have shown complete tumour regression following the eradication of *Helicobacter pylori* infection from the patient's stomach (8).

The aim of the work is to evaluate the efficacy of surgical resection followed by chemotherapy in patients with early stages gastric lymphoma. We studied the clinicopathological data, treatment results and survival of patients with PGL.

PATIENTS & METHODS

Thirty patients with a histologically confirmed primary gastric non-Hodgkin's lymphoma stage I_E, II_{1E} and II_{2E} according to Ann Arbor staging system as modified by Musshoff's criteria were treated with combined modality including surgery followed by chemotherapy between January 1991 and August 1997 in the Department of Surgical Oncology and Clinical Oncology and Nuclear Medicine, Mansoura University. The clinical, surgical and histopathological data of all the patients are shown in table (1). According to the working formulation, 8 patients had high grade histologic subtype, 16 patients had intermediate grade and 6 patients had low grade (Table 2). All patients underwent gastrectomy (13 distal subtotal and 17 total gastrectomy), as shown in table (3). Splenectomy had been done in 10 cases and distal pancreatectomy in 3 cases due to the low rate of accuracy of the preoperative diagnostic endoscopic biopsies. Also, resection of a part of

the transverse colon was done in 2 cases and part of the small intestine in other two cases. The resection permitted complete surgical staging utilizing pathological features, negative/positive regional lymph node and negative/positive surgical margins. If there was no evidence of these pathologic factors the patients who underwent surgery alone received no further chemotherapy and is happened in 4 patients who were subsequently excluded. All patients were treated with adjuvant chemotherapy for 6 courses repeated every 3 weeks. CVP (cyclophosphamide 750 mg/m² I.V. day 1, vincristine 1.4 mg/m² I.V. day 1 and prednisolone 100 p.o. for 5 days) for low grade subtype and CHOP (cyclophosphamide 750 mg/m² I.V. day 1, vincristine 1.4 mg/m² I.V. day 1, doxorubicin 50 mg/m² I.V. day 1 and prednisolone 100 p.o. for 5 days) for intermediate and high grade patients. Response to treatment was assessed according to WHO criteria, 3 months after the end of treatment using CT abdomen. The median follow-up period was 60 months ranging from 30-80 months. The overall 5 year survival rate was calculated for all patients as well as for the subgroups with curative and non-curative resections, and the 5 year disease free survival was calculated with staging using the Kaplan Meier method. Toxicity to systemic chemotherapy was graded according to WHO criteria.

RESULTS

In this study thirty patients with PGL, with a median age of 50 years (range 32-65), 18 were males and 12 were females. In our series primary gastric lymphoma was defined as a localized disease i.e. I_E (n=13), II_{1E} (n=7) and II_{2E} (n=10). According to Working Formulation the patients were classified into low grade (n=6), intermediate (n=16) and high grade (n=8), the

different histologic subtypes were shown in table (2). A curative resection was performed in 16/20 (80%) of patients with stage I_E or II_{1E} while this rate was 4/10 (40%) for stage II_{2E} patients. Survival was significantly correlated to the type of resection, patients who underwent a curative resection had a significant higher overall 5 year survival than those who underwent a non-curative resection (80% versus 40%, p<0.01 as shown in Fig. 1). Complete response (CR) rate was 93.3%. All stages I_E and II_{1E} achieved complete response (100%) while 8 patients (80%) of stage II_{2E} had CR and 2 patients had partial response (20%) (table 4). The five year disease free survival was 92% for stage I_E and 86% for stage II_{1E} while it was 60% for stage II_{2E}. The survival was significantly correlated to the stage (P<0.05 as shown in Fig. 2). The overall progression free survival rate was 80% at

5 years with a median of 48 months as shown in Fig. (3).

Haematological toxicity and nausea and vomiting were mild (grade 1 & 2) while other toxicity included diarrhea, alopecia and peripheral neuropathy were of grade 1 as shown in table (5).

Most of the complications of systemic chemotherapy were acceptable and can be overcome by suitable preparation of the patients, assurance and treatment of some complications as diarrhea and anemia.

Two cases after S-pouch developed fistulae and were managed conservatively and one case developed subphrenic collection and needed surgical drainage after failure of ultrasonic drainage

Table (1) : Patient characteristics.

Variable	No. of patients
* Total No. of patients.	30
* Median age (range)	50 (32 - 65)
* Sex: male/ female	18/12
* Tumor location :	
Upper 1/3	5
Middle 1/3	6
Distal 1/3	13
Whole stomach	6
* Uniform lesion	27
* Multifocal	3
* Stage (Ann Arbor Musshoff):	
I _E	13
II _{1E}	7
II _{2E}	10
Total	30

Table (2) : Grading according to working formulation.

Variable	Working formulation	No. of patients
* Low grade.	- Small lymphocytic.	2
	- Follicular mixed cell	4
* Intermediate grade.	- Follicular large cell.	4
	- Diffuse mixed cells.	8
	- Diffuse large cells.	4
* High grade.	- Large cell immunoblastic.	3
	- Lymphoblastic.	5

Table (3) : Treatment modalities.

Variable	No. of patients
* Type of gastrectomy :	
Total gastrectomy.	17
Subtotal gastrectomy	13
* Extent of operation:	
Splenectomy.	10
Distal pancreatectomy.	3
Other.	4
* Chemotherapy :	
CVP	6
CHOP	24

Table (4) : Response rate according to staging.

Staging	No. of patients	CR	%	Staging	
				No.	%
Stage IE	13	13	100%	-	-
Stage II1E	7	7	100%	-	-
Stage II2E	10	8	80%	2	20
Total	30	28	93.3%	2	6.7

CR = Complete response PR = Partial response.

Table (5) : Toxicity of systemic chemotherapy according to WHO.

	Grading				
	0	1	2	3	4
* Haematological :					
- Anaemia.	20	8	2	-	-
- Leucopenia.	15	11	4	-	-
- Thrombocytopenia.	22	6	2	-	-
* Nausea & Vomiting.	24	4	-	-	-
* Diarrhea.	24	6	-	-	-
* Peripheral neuropathy.	20	10	-	-	-
* Alopecia.	6	24	-	-	-
* Cardiomyopathy.	-	-	-	-	-

DISCUSSION

The management of early stage gastric lymphoma remains controversial. Multimodality approach, surgery followed by chemotherapy or radiotherapy was the therapy of choice for early stage I_E and II_E gastric lymphoma. The pre-operative diagnostic accuracy rate in this study is low, this explains the relatively high rate of combined splenectomy or resection of neighbouring organs since in about 50% of the patients the diagnosis was anaplastic carcinoma of the stomach by pre-operative endoscopic biopsies.

The quality of resection in this study had an important prognostic indicator, although all patients received postoperatively adjuvant chemotherapy. It was significantly lower in those patients with residual disease after surgery compared to patients who underwent a complete resection. The bulky disease required extended gastrectomy, splenectomy and resection of neighbouring organs, which increased surgical complications and mortality (Fig. 4).

In this study, survival was correlated with the quality of resection which has a significantly higher 5-year disease free survival in curative

resection than those who underwent non-curative resection, these findings are similar to that obtained by Roukos et al. (9).

Complete response rate for treatment was 93.3% for all patients and 80% for stage II_{2E}. These results are identical to that reported by Zingani et al. (1).

In this study, combination chemotherapy was well tolerated, toxicity was mild including mainly alopecia, leucopenia, peripheral neuropathy and anaemia which did not prevent treatment continuation. Grade 3 or 4 toxicity were not reported. These findings are similar to that obtained by Zingani et al. (1). In this series, the progression free survival rate was 80% at 5 years with a median of 48 months. These results were in agreement with those reported by Zingani et al. (1).

There was a statistically significant correlation between disease free survival and staging. These findings are comparable to those obtained by Bartlett et al. (5).

Surgery can rarely achieve a curative resection for stage II_{2E} patients, since a curative resection is a strong prediction for patient outcome and chemotherapy is associated with a

relatively high response rate. In unresectable lesions, the available treatment results with primary surgery and chemotherapy are controversial (10).

CONCLUSION

Total or subtotal gastrectomy and extensive lymph node dissection followed by chemotherapy for early stage I_E or II_{1E} primary gastric lymphoma is necessary, safe and offers long term survival. The optimal treatment for advanced stage or II_{2E} PGL is unknown and need further study with a larger number of patients.

Our study confirms the efficacy of surgery and chemotherapy combination in obtaining good remission rate for localized early primary gastric lymphoma and indicates that this combination represents the only means for managing complications.

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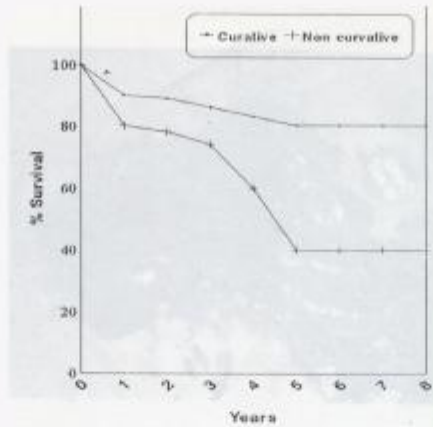


Fig. (1): Survival curves of patients with a primary stage I, II_{1E} and II_{2E} gastric lymphoma after curative or non-curative resection.

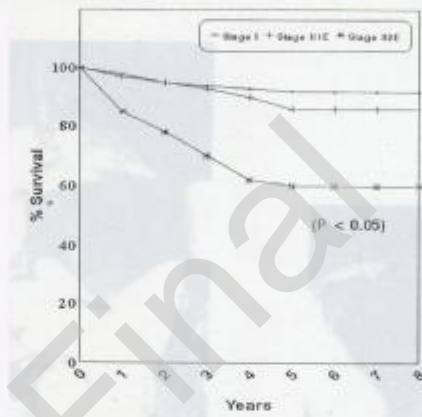


Fig. (2): Disease free survival of patients with a primary gastric lymphoma for stage I & II_{1E} and II_{2E}.

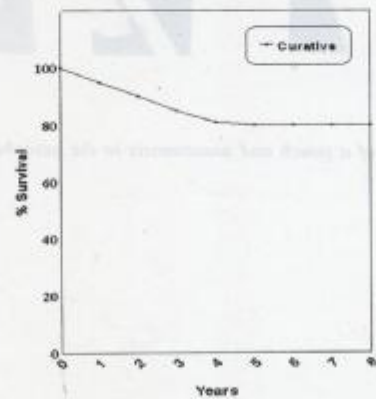


Fig. (3): Progression free survival.



Fig. (4): Specimen of gastric lymphoma.



Fig. (5): Creation of a pouch and anastomosis to the oesophagus after total gastrectomy.