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Chemotherapy for early-stage gastrointestinal lymphoma*

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Summary. A total of 176 patients with gastrointestinal lymphomas were reviewed. According to a modified staging classification, 51 of them had stage I/II disease and the remaining 125 had stage III/IV disease. In most cases (68%), the histology was intermediate-grade according to the NIH working formulation, and the B-cell immunophenotype was involved in 89% of the 45 cases with a known immunophenotype. The primary site was the stomach in 56% of cases and the bowel in 44%. A significantly higher proportion ($P = 0.001$) of those with bowel lymphomas had stage III/IV disease (88% vs 57%). The primary gastrointestinal lesion was resected in 122 patients, including all 51 cases of stage I/II disease. In all, 8 stage I/II patients were given radiotherapy alone following surgery and the other 43 underwent chemotherapy; of the latter, 19 received additional radiotherapy following chemotherapy. Chemotherapy was also given to 112 stage III/IV patients, 42 of whom underwent additional radiotherapy. Factors associated with a poorer prognosis included advanced disease, bowel lymphoma and advanced age. Although the complete response (CR) rate according to disease stage was similar, stage I/II patients receiving chemotherapy showed a significantly lower relapse rate, better disease-free survival following CR and improved survival as compared with those receiving radiotherapy alone. However, additional radiotherapy following chemotherapy did not further improve the clinical outcome.

Introduction

The gastrointestinal tract is a common site for extranodal lymphoma, and gastrointestinal lymphoma accounts for almost 18% of all cases of non-Hodgkin's lymphoma in Hong Kong Chinese [3, 9]. The Ann Arbor staging classification has been found to be unsatisfactory when applied to gastrointestinal lymphoma; modifications have been suggested to obtain better correlation with prognosis [4]. In a previous analysis, we have shown that a modified staging classification according to Crowther et al. [4] can quite well stratify patients with gastrointestinal lymphomas into two subgroups of localised (stages I and II) and advanced (stages III and IV) disease, which correlate very well with the prognosis [4, 14] (Table 1). However, the optimal therapy for patients with localised gastrointestinal lymphoma remains uncertain. The relative roles of surgery, radiotherapy and chemotherapy remain to be defined [14]. This paper presents a retrospective analysis of 176 patients with gastrointestinal lymphomas and assesses the efficacy of chemotherapy in treating patients with localised stage I/II disease following surgery.

Patients and methods

From January 1975 to December 1988, 176 patients attending the Department of Medicine, Queen Mary Hospital, University of Hong Kong,

Table 1. A modified staging classification for gastrointestinal lymphomas

I a	Tumour confined to one area of gastrointestinal tract without penetration of serosa
I b	Multiple tumours confined to gastrointestinal tract without penetration of serosa
II a	Tumour with regional lymph nodes histologically involved (gastric or mesenteric)
II b	Tumour with perforation and/or adherence to adjacent structure
II c	Tumour with perforation and peritonitis
III	Tumour with widespread nodal involvement (para-aortic or more distant nodes)
IV	Disseminated disease involving other extralymphatic tissues not adjacent to the tumour (e. g. liver, marrow, bone, lung)

According to Crowther and Rankin [4]

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Table 2. The clinical outcome of 176 patients with gastrointestinal lymphoma

		CR		Relapse		DFS(CR patients) 5-year	DFS(CR patients) Median	SUR (all patients) 5-year	SUR (all patients) Median
A	Sex:								
	Male	59/90	(66%)	14/59	(24%)	54%	NR	44%	27 months
	Female	51/86	(59%)	17/51	(33%)	44%	62 months	49%	28 months
	P-value	NS		NS		NS		NS	
B	Age:								
	>60 years	40/69	(58%)	14/40	(35%)	38%	46 months	39%	22 months
	<60 years	70/107	(65%)	17/70	(24%)	61%	NR	51%	NR
	P-value	NS		NS		NS		0.03	
C	Histological subtypes:								
	Low-grade	8/14	(57%)	2/8	(25%)	50%	42 months	59%	67 months
	Intermediate-grade	82/119	(69%)	24/82	(29%)	53%	62 months	49%	40 months
	High-grade	9/18	(50%)	3/9	(33%)	60%	NR	30%	15 months
	P-value	NS		NS		NS		NS	
D	Clinical staging:								
	I/II	42/51	(82%)	4/42	(10%)	74%	NR	80%	NR
	III/IV	68/125	(54%)	27/68	(40%)	42%	31 months	35%	16 months
	P-value	0.001		0.0014		0.0003		0.0001	
E	B symptoms:								
	A	70/111	(63%)	17/70	(24%)	56%	NR	45%	28 months
	B	40/65	(62%)	14/40	(35%)	45%	62 months	50%	27 months
	P-value	NS		NS		NS		NS	
F	Primary sites:								
	Stomach	67/98	(68%)	13/67	(19%)	62%	NR	54%	67 months
	Bowel	43/78	(55%)	18/43	(42%)	42%	27 months	37%	16 months
	P-value	NS		0.025		NS		0.04	
G	Overall	110/176	(63%)	31/110	(28%)	54%	62 months	46%	28 months

CR, Complete remission; DFS, disease-free survival; NR, not reached; NS, not significant; SUR, overall survival

were diagnosed as having gastrointestinal lymphoma, which was defined as the presence of predominantly gastrointestinal lesions or symptoms that were histologically proven to have been caused by lymphoma [3]. The pathological materials were reviewed and classified according to the NCI working formulation [17]. Fresh tissue specimens were available from 45 cases (26%) for immunophenotyping [10].

Patients were staged using a modified classification according to Crowther and Rankin [4]. Clinical staging procedures included physical examination, chest radiograph, full blood counts, blood biochemistry, iliac-crest trephine biopsy and aspirate of bone marrow. Lymphography and/or computerized axial tomography were performed to look for abdominal lesions. Barium studies or endoscopy with biopsy were used to define the gastrointestinal lesions, and a laparotomy was performed in 138 of them (78%).

Tumour responses were assessed using standard criteria [11]. The Kaplan-Meier product-limit method was used to generate disease-free survival (DFS) curves [12]. DFS time was measured from the date of first remission to the date of first relapse. The overall survival was measured from the date of diagnosis to the date of death or last follow-up. The log-rank procedure was used to compare survival curves, and the chi-square test with Yates' correction was used to compare complete response (CR) and relapse rates.

Results

Patients' characteristics

There were 90 men (51%) and 86 (49%) women; the median age was 55 years (range, 14–92 years). Lymphomas in 35 (20%) patients were classified as stage I (32, Ia; 3, Ib); in 16 (9%), as stage II (12, IIa; 2, IIb; 2, IIc); in 31 (18%, as stage III; and in 94 (53%), as stage IV. Overall, 65 patients (37%) had B symptoms and 40 (23%), bulky disease.

The histological subtypes were low-grade in 14 (8%) cases (small lymphocytic in 6, follicular small-cell in 4, follicular mixed in 4), intermediate-grade in 119 (68%) patients (follicular large-cell in 3, diffuse small cleaved-cell in 15, diffuse mixed in 20, diffuse large-cell in 81), high-grade in 18 (10%) subjects (diffuse immunoblastic in 13, diffuse lymphoblastic in 2 and diffuse small non-cleaved-cell in 3), and unclassifiable in 25 (14%) cases. Immunophenotyping was performed in 45 cases. In all 40 (89%) cases involved B-cell lymphoma and 1 (2%) had T-cell lymphoma; 4 (8.9%) cases were inconclusive.

The primary site of disease was the stomach in 98 (56%) patients, the small bowel in 44 (25%), the ileocecal region in 13 (7.4%) and the large bowel in 21 (12%). A significantly higher proportion ($P = 0.001$) of patients with bowel lymphomas had advanced stage III/IV disease (69/788, 88%) as compared with those with gastric lymphomas (56/98, 57%).

Treatment and clinical outcome

Surgical resection of the primary gastrointestinal lesion was performed in 122 patients, including all 51 patients with stage I/II disease. In all, 8 stage I/II patients received radiotherapy and 155 underwent chemotherapy; 61 sub-

Table 3. The clinical outcome of patients with gastrointestinal lymphomas according to the modes of therapy and stage of disease

	CR		Relapse		DFS (CR patients) 5-year	DFS (CR patients) Median	SUR (all patients) 5-year	SUR (all patients) Median
Stage I/II disease								
Radiotherapy vs chemotherapy:								
Radiotherapy alone	7/8	(88%)	3/7	(43%)	44%	58 months	50%	28 months
Doxorubicin-containing chemotherapy	25/29	(86%)	0/25	(0)	100%	NR	91%	NR
Other chemotherapy	10/14	(71%)	1/10	(10%)	89%	NR	87%	NR
P-value	NS		0.003		0.05		0.02	
Chemotherapy vs chemotherapy + radiotherapy:								
Chemotherapy + radiotherapy	15/19	(79%)	0/15	(0)	100%	NR	89%	NR
Chemotherapy alone	20/24	(83%)	1/20	(5%)	93%	NR	87%	NR
P-value	NS		NS		NS		NS	
Stage III/IV disease								
Doxorubicin-containing chemotherapy	54/75	(72%)	24/54	(44%)	38%	28 months	41%	24 months
Other chemotherapy	14/37	(38%)	3/14	(21%)	66%	45 months	32%	12 months
P-value	0.001		NS		NS		NS	

CR, Complete remission; DFS, disease-free survival; NR, not reached; NS, not significant; SUR, overall survival

jects were given additional radiotherapy following chemotherapy. A total of 13 stage III/IV patients received neither chemotherapy nor radiotherapy because of either very poor performance status or patient refusal. Doxorubicin-containing regimens were used in 104 patients with intermediate- and high-grade histology[1]: CHOP in 59, BACOP in 42 and m-BACOD in three [16, 19, 22]. Less intensive chemotherapy regimens were used in the other 51 patients because of advanced age or poor cardiopulmonary function in 37 cases and low-grade histology in 14 subjects: (19 patients received COPP; 14, CVP; 18, other regimens) [1, 5].

In all, 8 stage I/II patients received local radiotherapy only and the other 43 underwent chemotherapy; of the latter, 19 were given additional radiotherapy following chemotherapy. A total of 112 stage III/IV patients underwent chemotherapy, 42 of whom received additional radiotherapy following chemotherapy.

The clinical outcome of all 176 patients is shown in Table 2. Those with stage I/II disease had a significantly higher CR rate, a lower relapse rate, better DFS following CR and superior survival as compared with patients who had stage III/IV disease. As compared with those who had gastric disease, patients with bowel lymphomas had a significantly higher relapse rate following CR and worse survival. Patients of advanced age also showed significantly poorer survival.

Table 3 shows the clinical outcome according to the modes of therapy and the stage of disease. Although the CR rates were similar, patients with localised gastrointestinal lymphomas who reveived doxorubicin-containing or other chemotherapy had a significantly lower relapse rate, better DFS following CR and superior overall survival as compared with those who were given radiotherapy alone. However, additional radiotherapy following chemotherapy did not further improve the clinical outcome of our stage I/II patients. Because of the small number of subjects with stage Ib, IIb and IIc disease, it was not possible to determine the prognostic effect of multiple tumours confined to the gastrointestinal tract (Ib), penetration of tumour through the serosa (IIb) or perforation with peritonitis (IIc) in patients with otherwise localised gastrointestinal lymphomas [4].

Discussion

The median age of our 176 patients with gastrointestinal lymphoma was 55 years and there was a roughly equal sex distribution [6, 8, 18, 21, 24]. A majority (71%) of them had advanced stage III/IV disease according to the modified classification. The histology was mostly intermediate-grade according to the NIH working formulation, and the B-cell immunophenotype was almost always involved. The stomach was the most common primary site, and patients with bowel lymphoma more often had advanced disease. Subjects with advanced disease, primary bowel disease and advanced age were associated with a poorer prognosis [14].

Surgery has played an important role in the management of patients with gastrointestinal lymphomas [6]. Although the diagnosis of gastric lymphomas can often be made using endoscopy, laparotomy is often necessary to obtain a precise tissue diagnosis in intestinal lymphomas. Laparotomy also enables accurate staging of the disease, which determines the prognosis. Furthermore, there is evi-

[1] CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; BACOP, bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone; m-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone

dence suggesting that adequate surgical debulking may significantly improve survival. Although surgery alone may be curative in occasional patients with truly localised disease, the relapse rate is expected to be >50% if surgery only is used, even in patients with stage I/II disease [6, 8, 18, 21, 24]. However, surgical resection of the primary gastrointestinal lesion is often recommended, as it is useful in preventing chemotherapy- or radiotherapy-induced hemorrhage or perforation [6, 14].

Although cure is possible in patients with localised gastrointestinal lymphomas through the use of abdominal irradiation following complete surgical resection, recurrence is frequent and often occurs outside the irradiation treatment field [2, 7, 8, 13, 15, 18, 20, 21, 23, 24]. The proportion of patients remaining in remission at 5 years following surgery and radiotherapy has been reported to range from 33% to 85% [20]. Recent studies have suggested that the use of chemotherapy following surgery prevents relapses and improves the survival of these patients [20, 23]. However, whether additional radiotherapy is necessary following chemotherapy remains uncertain [20].

All of our 51 stage I/II patients were staged by laparotomy and had their primary gastrointestinal lesions resected. Only 8/51 (16%) were treated with radiotherapy alone; as compared with those receiving chemotherapy, patients undergoing radiotherapy only had a significantly higher relapse rate, shorter DFS following CR and poorer survival. However, additional radiotherapy following chemotherapy did not appear to improve further the prognosis.

The intrinsic problem of this kind of retrospective analysis is well recognised and it remains impossible to draw a definite conclusion regarding the treatment of early-stage gastrointestinal lymphomas. However, this study has provided valuable information for the planning of future prospective trials. For patients with stage I/II disease, the necessity of surgical resection and the optimal therapy following surgery (radiotherapy alone vs chemotherapy alone vs chemotherapy plus radiotherapy) remains to be determined by prospective randomised study.

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