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Combination Chemotherapy for Primary Small Intestinal Lymphoma in the Middle East

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Abstract—*Twelve patients with primary small intestinal lymphoma were followed prospectively for 3 years. Endoscopic abnormalities were diagnostic of lymphoma in all cases where the duodenum was involved* (83%). *In three cases* (25%) *the disease extended to the stomach. One patient* (8%) *had diffuse small cell cleaved and* 11 (92%) *diffuse large cell lymphoma stages I* (8%), *II* (25%), *III* (58%) *and IV* (8%). *Nine of them were unresectable and primarily treated with combination chemotherapy*; 67% *achieved complete remission*, 22% *partial response and* 11% *no response. Only one patient relapsed and achieved a second remission. All complete remission patients are currently alive and free of disease at a median follow-up of* 36 *months. Overall survival for all patients is* 58%, *and disease-free survival is* 50%. *No instance of chemotherapy-related bleeding or perforation was seen. Tetracycline was necessary for the treatment of IPSID-associated diarrhea and malabsorption in spite of cytotoxic chemotherapy.*

INTRODUCTION

EXTRANODAL small intestinal lymphoma is a relatively common neoplasm in the Middle East [1–11]. Its relationship to premalignant immuno-proliferative small intestinal disease (IPSID), which may be present in up to 50% of the cases, has been well described [2, 5–8]. Patients usually present with advanced disease and have high grade histology [2, 5–8]. Associated gastric involvement is only very rarely seen [12]. Although its pathological aspects have been well studied [6, 8, 10, 11, 13–16], reports on its response to chemotherapy are few [5, 7, 8, 16], including series from Western centers [17–19]. In this report we present a study of 12 patients that we saw over a period of 2 years in Saudi Arabia in a primary and referral university hospital operating since 1981 and which has had an oncology service since 1984. We summarize our patient characteristics and report our results with combination chemotherapy providing follow-up data of 3 years.

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PATIENTS AND METHODS

Patients

Between January 1985 and February 1987, 26 adult patients with gastrointestinal lymphoma were seen at King Khalid University Hospital in Riyadh, Saudi Arabia; 11 patients had gastric lymphoma and 15 had small intestinal lymphoma. Of the latter, 12 patients were considered to have primary small intestinal lymphoma according to the criteria described by Lewin *et al.* [20], either when there is obvious predominant gastrointestinal tract lesions or when initial presentation with gastrointestinal symptoms is proved to be caused by gastrointestinal involvement with lymphoma. Lymphoma was considered of the 'Western' (West.) type when there was limited involvement of the gastrointestinal tract, and 'Mediterranean' (Medit.) type when there was diffuse involvement [9, 11]. Patients were followed prospectively and data were collected until July 1988.

Diagnosis, classification and staging

All patients had routine blood counts, renal and liver function chemistries, protein electrophoresis and immuno-electrophoresis, *d*-xylose test, 72-h stool fat, bone marrow aspirate and biopsy, chest and abdominal plain X-rays, barium meal (upper gastro-intestinal series) with small bowel follow-through, small bowel enema, abdominal ultrason-

ography, abdominal CAT scanning, and esophago-gastro-duodenoscopy (EGD). During EGD, multiple step biopsies were taken from and around all suspicious lesions as well as the entire gastrointestinal scoped areas. Biopsy specimens were processed for routine hematoxylin and eosin stains, immunoperoxidase stains and electron microscopy. Diagnosis was obtained by laparotomy when histology remained inconclusive or in cases of abdominal emergency. Histological classification was based on the International Working Formulation [21]. Diagnosis of immunoproliferative small intestinal disease (IPSID) was based on the criteria of Salem *et al.* and others [2, 5–8]. The application of the Ann Arbor staging system [22] was unsatisfactory and the following modified staging system [5, 23–26] was used:

Stage I: Lymphoma strictly limited to small intestinal mucosa and wall.

Stage II: Lymphoma with limited involvement of mesenteric lymph nodes.

Stage III: Lymphoma with extensive involvement of mesenteric lymph nodes, or involvement of retroperitoneum, pancreas or para-aortic lymph nodes.

Stage IV: Presence of distant disease.

Treatment

Surgical exploration was performed in emergencies and in cases of inconclusive diagnosis, and intestinal resection was performed in cases of limited jejunal disease. No major surgery was attempted for duodenal lymphoma and it was considered unresectable. Radiotherapy was not used as a primary treatment in any patient. Combination chemotherapy (CT) was the primary tool of treatment. All patients with diffuse large cell lymphoma seen before September 1985 were treated with m-BACOD [27], and those seen afterwards with CHOP-Bleo [28]. One patient had C-MOPP [29], a non-doxorubicin containing regimen, because of jaundice. Chemotherapy was given for six cycles or until two cycles after documented complete remission. The patient with diffuse small cell cleaved lymphoma received additional chlorambucil and prednisone. All patients were given antacids and ranitidine. Intravenous hyperalimentation was given to cachectic and debilitated patients. Tetracycline was added to treat IPSID-associated diarrhea and malabsorption. It was given for a period of 2 years.

Criteria for response and follow-up

Complete remission (CR) was defined when either all clinical, radiological, endoscopic and histological signs of lymphoma disappeared, or in the absence of lymphoma on repeated histological examinations in spite of residual radiological and endoscopic abnormalities in patients who are in clinical remission. Remission duration is measured from the time of CR until relapse, death or last follow-up. Survival is calculated from time of diagnosis until death or last follow-up. Patients were followed with complete physical examination, blood counts, liver and renal function tests, monthly during chemotherapy and 3-monthly aftewards. Endoscopy was performed during the first year every 3 months and every 6 months afterwards. Barium meal, small bowel enema, abdominal ultrasound and abdominal CAT scan were done every 6 months during the first 2 years, and yearly afterwards.

RESULTS

Patient characteristics

Ten patients (83%) were males and two (17%) were females. Their median age was 32 years (range: 21–58). All patients were Arab nationals. Six were Saudis, three Yemenis, and one each from from Egypt, Sudan and Tunisia.

All patients were severely ill and 25% had abdominal emergencies at presentation. Duration of symptoms varied between 1 and 36 months (average 13 months). Patients presented with abdominal pains (91%), nausea and vomiting (50%), hematemesis (17%), melena (33%), weight loss (100%), fever (25%), palpable abdominal masses (17%), obstructive jaundice (17%), and small intestinal obstruction (17%).

The duodenum was involved in 83% of the cases. Five patients (42%) had lymphoma limited to the duodenum, two patients (17%) had disease of duodenum and jejunum, one patient (8%) had disease of jejunum only, one patient (8%) had disease of jejunum and ileum, and three patients (25%) had disease extending into the stomach.

Three patients (25%) were considered to have the 'Western' type of lymphoma and nine patients (75%) the 'Mediterranean' type.

Eleven patients (92%) had a high grade diffuse large cell lymphoma and one patient (8%) had an intermediate grade diffuse small cell cleaved lymphoma. Six patients (50%) had a diffuse lympho-plasmacytic infiltrate (DLPI) of whom only three patients (25% of total) had clinical features of IPSID.

According to the modified staging system described above, one patient (8%) had stage I, three patients (25%) stage II, seven patients (58%) stage III, and the one patient (8%) with small cell cleaved histology had stage IV.

A summary of patient characteristics is given in Table 1.

Remission induction and duration

Of the nine patients with diffuse large cell lymphoma treated primarily with chemotherapy six patients (67%), two stage II and five stage III,

Table 1. *Summary of patient characteristics and therapy*

Patient No.	Sex	Age	DLPI	IPSID	Type	Histology	Stage	Therapy	Response	Follow-up
1	M	25	No	No	West.	D L C	III	m-BACOD	PR	Lost
2	M	26	Yes	Yes	Medit.	D L C	III	m-BACOD	CR/relapse 2nd CR	Alive
3	M	21	Yes	No	Medit.	D L C	III	m-BACOD	CR	Alive
4	M	31	No	No	Medit.	D L C	III	m-BACOD	CR	Alive
5	F	35	Yes	Yes	Medit.	D L C	III	CHOP-Bleo	CR	Alive
6	M	48	Yes	Yes	Medit.	D L C	II	CHOP-Bleo	CR	Alive
7	M	36	Yes	No	Medit.	D L C	II	CHOP-Bleo	CR	Alive
8	F	28	No	No	Medit.	D L C	III	CHOP-Bleo	No response	Dead
9	M	45	Yes	No	Medit.	D L C	III	C-MOPP	PR/lost/relapsed	Alive
10	M	50	No	No	West.	D L C	I	Surgery/adjuvant CT	CR/relapse	Dead
11	M	27	No	No	Medit.	D L C	II	Surgery (unresectable)	None	Dead
12	M	58	No	No	West.	S.C.Cl	IV	m-BACOD/chlorambucil	CR	Lost

For abbreviations, see text.

went in complete remission and remain alive free of disease (five in continuous first remission and one in second remission from a first relapse at 15 months) at the time of this report; their complete remission duration varies between 21 and 32 months (median: 29 months), and their overall survival duration varies between 30 and 39 months (median: 36 months). Two patients (22%) had a partial response (PR) and were lost to follow-up after three cycles of chemotherapy; one of them returned with a local relapse after 13 months and is currently receiving chemotherapy while the other is considered as a non-survivor for the rest of the analysis. One patient (11%) died of progressive disease at 2 months of chemotherapy.

Of the other three patients, one died of continuous bleeding at presentation, one was treated primarily with jejunal resection and received adjuvant chemotherapy, relapsed and died at 15 months of CR, and one (with small cell cleaved histology) had a CR after a year of treatment with m-BACOD followed by chlorambucil and prednisone and disappeared to further follow-up and therefore considered as a non-survivor for the rest of the analysis.

Responses of m-BACOD and CHOP-Bleo are similar.

Responses and patient characteristics are summarized in Table 1.

Overall survival at 3 years is 58% (Fig. 1A), considering 17% lost to follow-up in excellent condition as non-survivors. Disease-free survival at 3 years is 50%.

Overall and disease-free survival of the nine patients with diffuse large cell lymphoma who received only chemotherapy is 78% (Fig. 1B).

The addition of tetracycline resulted in the prompt resolution of diarrhea and malabsorption in three patients, one at the beginning of chemotherapy and two after 3 months of chemotherapy and persistence of severe diarrhea.

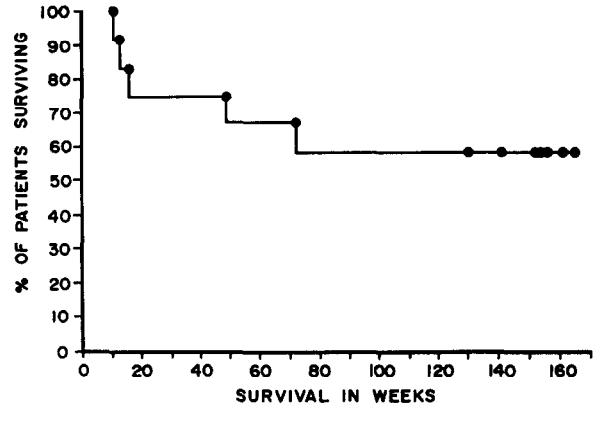

Fig. 1*A. Survival of all patients.*

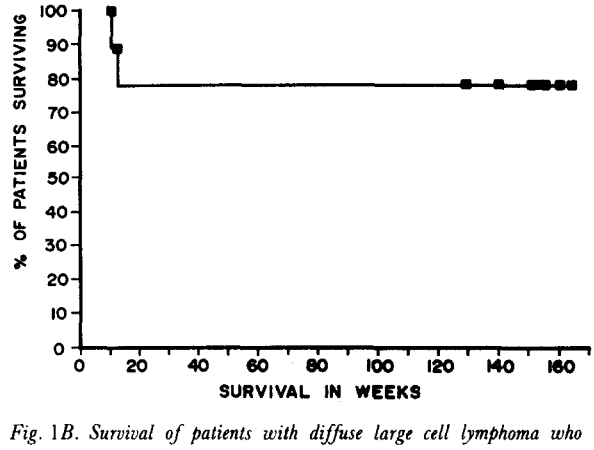

Fig. 1*B. Survival of patients with diffuse large cell lymphoma who received chemotherapy only.*

Complications

All patients had mild to moderate nausea and vomiting. Severe peripheral neuropathy with satisfactory recovery was seen in one patient. All patients had alopecia with subsequent recovery. One patient had Adriamycin® extravasation requiring a skin graft. Severe neutropenia with fever was seen in two patients. No life-threatening infections occurred. No

patient had bleeding or perforation from small intestinal lymphoma secondary to chemotherapy.

DISCUSSION

Our patient characteristics are similar to other observations from the Middle East but with a lower incidence of a full picture of IPSID (with diarrhea and malabsorption) at 25% only although a DLPI was seen in 50% of the patients. We had a predominance of males, and patients presenting with long standing symptoms, advanced disease and high grade diffuse large cell histology.

Most reports on chemotherapy for small intestinal lymphoma of the Middle East, in the English medical literature, date from the last decade and show results of single agents or combinations of cyclophosphamide, vincristine and predinsone [5–9, 16, 24, 30, 31]. Some authors reported a limited experience with a generally poor outcome [7], or a high death rate with a high number of patients lost to follow-up [5]. Although one relatively recent review [8] concludes that IPSID-associated lymphoma can be successfully treated with chemotherapy, other recent authors reported or concluded that the prognosis is generally poor [11, 24, 32], especially in cases associated with IPSID and malabsorption [24] with most patients relapsing and dying within 1–2 years [24] or 3 years [32] from diagnosis, and with 5-year survival rates of 22.70% [11]. A recent retrospective study [9] included results of chemotherapy, mostly cyclophosphamide, vincristine and prednisone combinations, often combined with surgery and or radiotherapy in 108 cases with predominant lymphocytic lymphoma, and showed an overall 2-year survival rate of 48%, and 5-year survival rate of 29% for proximal small intestinal disease.

Reports from western centers are usually retrospective studies extending over years or decades [17–20, 25, 33, 34]. Recent reports emphasize the role of surgical resection [18, 34] and chemotherapy [18].

Most of our patients had diffuse disease of the gastrointestinal tract and in cases where disease was limited to a small portion of the jejunum it was resected; however, no attempt was made at extensive duodenal resection.

Our observed responses to chemotherapy as the single and primary tool of therapy (67% CR, 22% partial response and 11% failure) with all complete responders currently alive and free of disease at 3 years are very encouraging. Contrary to observations referenced above [24, 32], we did not find a poorer response in patients with associated IPSID. Our three patients with documented IPSID went in CR and are all currently among disease-free survivors (two in first CR and one in second CR). Intravenous hyperalimentation enabled us to deliver chemotherapy for debilitated patients without delay.

For the entire group of 12 patients, it is also encouraging to note that the overall survival of 58% and disease-free survival of 50%, including one patient (8%) who died of bleeding before getting any treatment, and two patients (17%) who were lost to follow-up in excellent condition considered as non-survivors.

It is of interest to note that none of our 12 patients had chemotherapy-associated bleeding or perforation from diseased small bowel. These complications have been observed by some authors [25, 35, 36], and not observed by others [17, 37]. Herrmann *et al.* [17] noted one such occurrence outside their reported series, and we have recently seen a case of gastric lymphoma bleeding after chemotherapy (unpublished observation). Authors of series of 'Mediterranean' type of lymphoma have generally not mentioned bleeding and perforation [5–9, 24, 32] expect in one study [11] where a non-specific statement that "nearly all patients succumbed to a combination of malnutrition, mechanical problems (intestinal obstruction and/or perforation), sepsis, and bleeding" was made about a small number of patients treated with chemotherapy. We conclude that chemotherapy could be given to these patients without an exaggerated fear of secondary bleeding and perforation; however, close patient observation is mandatory as these complications have been described. Our systemic use of antacids and H2-blockers may have played an important role in preventing these complications.

It is also interesting to note that tetracycline was necessary to treat the diarrhea in IPSID-associated lymphoma cases in spite of lymphoma cytotoxic therapy. IPSID and its associated diarrhea and malabsorption represent a pre-malignant stage of lymphoma [5, 8, 30] the etiology of which is not well elucidated although an infectious associated agent is highly suspected. Our noted observation, as well as that of another patient with IPSID stage 0, without malignant lymphoma on histology who had no response to six cycles of m-BACOD and who had a complete clinical recovery only after we gave him tetracycline (unpublished observation), supports the idea that the etiologic agent may persist unchanged after the malignant transformation has occurred and that tetracycline therapy ought to be given in addition to cytotoxic chemotherapy in these cases.

In summary we conclude that combination chemotherapy can be reasonably safe and can give satisfactory remission and long term survival rates in patients with primary small intestinal lymphoma of the Middle East. The addition of tetracycline therapy remains essential for the management of associated IPSID.

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