Adjuvant Chemotherapy for Patients with Resected Dukes' C and High-risk B2 Colon Cancer with Fluorouracil and Levamisole

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Abstract

Carcinoma of the large bowel is the second leading cause of cancer mortality in Singapore. Although the great majority of patients are discovered at a stage where resection with curative intent is possible, almost half of the patients afflicted will die of it. The combination of 5-fluorouracil + levamisole used in patients with curatively resected high risk Dukes B2 and all Dukes' C colon cancers has been shown to reduce cancer recurrence rate and improve overall survival. Since 1990 adjuvant chemotherapy has been recommended for this group of patients. This report describes patients treated in Singapore, their toxicities and their outcome.

A total of 341 patients were treated between 1990 and 1996. Treatment compliance was 71.8%. Toxicity was moderate with mainly grade 1-2 nausea and vomiting, diarrhoea, stomatitis, alopecia, and neutropenia. There was 1 treatment-related death. Median recurrence-free interval was 81 months and median survival was not reached at 90 months. This regimen is tolerable. Until further randomised reports comparing 5-fluorouracil + levamisole to other combinations are available, this combination chemotherapy is recommended to patients after surgical resection of the high risk Dukes' B2 and Dukes' C colon cancer to reduce cancer recurrence and improve overall survival.

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Introduction

Carcinoma of the large bowel is the second leading cause of cancer mortality in Singapore. Although the great majority of patients are discovered at a stage where resection with curative intent is possible, almost half of the patients afflicted will die of it.[1] In 1989 the North Central Cancer and Treatment Group (NCCTG) published their evaluation of 5-fluorouracil + levamisole as adjuvant chemotherapy for large bowel carcinoma.[2] In their randomised study of 400 patients with Dukes' C and high-risk Dukes' B2 colorectal cancer, the combination of 5-fluorouracil and levamisole significantly reduced cancer recurrence rate by 31% and improved overall survival by 13%. In patients with Dukes' C large bowel cancer the overall death rate was significantly reduced by 5-fluorouracil and levamisole. Since then, numerous studies have confirmed the results of the NCCTG.[3-5] The current standard recommendation for patients with high-risk Dukes' B2 and Dukes' C large bowel carcinoma is adjuvant chemotherapy with 5-fluorouracil and levamisole.

This is a report of the experience by the Department of Medical Oncology in Singapore General Hospital of adjuvant 5-fluorouracil + levamisole in colon cancer patients between 1990 and 1996.

Patients and Methods

Between 1990 and 1996, all patients with high risk Dukes' B2 and C colonic carcinoma who fulfilled the eligibility criteria listed below were offered adjuvant 5-

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fluorouracil + levamisole. These patients were referred for adjuvant chemotherapy after colonic surgery. All patients were required to have had potentially curative resection of histologically confirmed adenocarcinoma of the colon. There could neither be gross nor microscopic evidence of residual cancer. High-risk cases required that the resected specimen showed one of the following indicators of poor prognosis: invasion into serosa or pericolonic fat, invasion of adjacent organs by direct extension, or metastases to regional lymph nodes. Patients with Dukes' B2 colon cancer were considered only if there was elevated preoperative carcinoembryonic antigen (CEA), presence of intestinal obstruction, tumour perforation or tumour adherence to adjacent organs at time of surgery. No patient could have had prior radiotherapy to the lumbar spine or pelvis or any prior 5-fluorouracil. Patients were ineligible if there was any other malignant disease within the previous 5 years except for superficial squamous or basal cell carcinoma of the skin or *in situ* cervix carcinoma. Patients were also required to have good Eastern Cooperative Oncology Group (ECOG) performance status not more than 2, adequate bone marrow, renal and liver function as defined by absolute neutrophil count greater than 1.5 x 10^9/L, platelet count greater than 100 x 10^9/L, serum creatinine less than 140umol/L, total bilirubin less than 35umol/L, alkaline phosphatase and alanine transaminase (ALT) or aspartate transaminase (AST) less than twice normal. Patients with evidence of distant metastases, recent history of myocardial infarction or severe active infection in the preceding 6 weeks, known history of allergy to 5-fluorouracil or levamisole were not eligible to receive the drugs. Patients with rectal or rectosigmoid carcinoma were excluded.

Chemotherapy

All patients were required to have a physical examination, full blood count, blood biochemistry, recent chest X-ray and liver ultrasonography or computerised tomography (CT) before commencing chemotherapy.

Patients received oral levamisole 40 mg four times a day for 3 days every other week for one year, starting on day 1. Intravenous bolus 5-fluorouracil 450mg/m^2 was administered daily for 5 days, then once a week starting from day 29 for one year. In patients where levamisole allergy was subsequently suspected, levamisole was discontinued and patients continued with 5-fluorouracil alone or in combination with leucovorin. Anti-emetics, oral mouth washes, and anti-diarrhoeal medication were not prophylactically administered. Full blood counts were obtained monthly while the patient was on chemotherapy. Upon completion of one year of therapy, all patients continued 3 to 4 monthly evaluation for 2 to 3 years, and subsequently, 4 to 6 monthly evaluations. At each visit, a full history was taken and patients underwent physical examination. Blood counts, biochemistry and CEA were performed at the physician's discretion. Chest X-ray was scheduled annually. Colonoscopy and liver ultrasonography were scheduled by the patients' respective surgeons.

Patient Characteristics

Between December 1990 and December 1996, 341 patients started adjuvant 5-fluorouracil + levamisole. Patient characteristics are shown in Table I. There were 191 males and 150 females. The median age was 57 years, with a range of 18 to 83 years. There were 33 patients aged 40 years or younger and 50 patients at least 70 years old at diagnosis. The majority of patients were Chinese and Dukes' C stage. Preoperative CEA was available for 201 patients and was elevated in 130 (64.6%) patients, range 3.6 to 177.0 ug/L.

TABLE I: PATIENT CHARACTERISTICS

Characteristic		Number of patients	%
Age			
Median (years)	57		
Range (years)	18 to 83		
Race			
Chinese		313	91.7
Malay		18	5.3
Indian		6	1.8
Others		4	1.2
Dukes' Stage			
B2		44	12.9
C		297	87.1
Depth of invasion			
Submucosa		4	1.2
Muscularis mucosa		6	1.8
Subserosa or pericolic fat		268	78.6
Perforates or invades adjacent tissue		40	11.7
Unknown		23	6.7
Number of nodes involved			
0		44	12.9
1-3		191	56.0
4 or more		97	28.5
Unknown		9	2.6

Results

The median follow-up since surgery for patients still alive was 30.4 months, range 0.6 to 90.9 months.

Ninety-two (27.0%) patients have recurred. Plot of recurrence-free interval for all patients is shown in Figure 1. Median recurrence-free interval was 81.2 months. Sites of initial recurrence were liver (42), lung (20), peritoneum (16), local anastomotic or regional lymph node site (16), bone (4), brain (2) and others (6). The number of lymph nodes involved by metastases was a

TABLE II: TOXICITIES OF CHEMOTHERAPY

Toxicity	Grade 0 (%)	Grade 1-2 (%)	Grade 3-4 (%)
Allergy	95.7	4.2	0
Alopecia	78.1	21.6	0.3
Dermatitis	87.7	12.3	0
Diarrhoea	69.2	26.7	4.1
Myalgia	96.7	3.3	0
Nausea, vomiting	54.8	43.7	1.5
Stomatitis	74.5	23.0	2.5
Neutropenia	54.4	30.6	15.0
Anaemia	77.7	21.6	0.7
Thrombocytopenia	91.0	8.3	0.7

Fig. 1. Plot of recurrence-free interval.

Fig. 2. Plot of overall survival.

significant predictor of recurrence. Age, sex, race, presence or absence of intestinal obstruction or perforation at surgery, preoperative CEA, differentiation of tumour, site of tumour and hospital where surgery was performed were all not significant predictors of recurrence.

Sixty-nine (20.2%) patients have died. There were 19 deaths without recurrence. Plot of survival is shown in Figure 2. Median survival for all patients has not been reached at 90 months. The race of the patient and the number of lymph nodes involved by metastases were significant predictors for survival. Age, sex, presence or absence of intestinal obstruction or perforation at surgery, normal or elevated preoperative CEA, differentiation of tumour, site of tumour, and hospital where surgery was performed were all not significant predictors of survival. After multivariate analysis, race was no longer a significant factor of survival.

Toxicity

The worst toxic reactions (ECOG criteria) throughout one year of chemotherapy are presented in Table II. Allergy, alopecia, dermatitis and stomatitis tended to occur during the first two months of therapy and were reversible. Nausea and vomiting, diarrhoea, myalgia and haematological side-effects could occur throughout the chemotherapy. Most toxicities tended to be mild. Of the non-haematological toxicities, 8 (2.4%) patients had grade 3-4 stomatitis requiring therapy or intravenous hydration. Stomatitis tended to be the most severe during the first cycle of therapy. Diarrhoea was mainly mild and transient, grade 1-2, and controlled with oral mediation. No patient required intravenous hydration for diarrhoea. Dermatitis, which could be due to levamisole allergy or 5-fluorouracil-induced phototoxicity, was present in 12.1% of patients. Of the haematological toxicities, anaemia and thrombocytopenia were mild in most patients. The majority of patients experienced grade 1-2 neutropenia. Although grade 3-4 neutropenia was seen in 15% of patients, there was only one treatment-related mortality (0.3%) due to neutropenic sepsis.

Treatment compliance was good. Most patients (71.8%) were compliant, continuing therapy for one year or until recurrence required discontinuation of therapy. Thirty-eight (11.1%) patients withdrew because of toxic reactions. Other patients withdrew because of concomitant medical conditions, such as cerebrovascular events or myocardial infarction unrelated to medication. Another 21 patients were continuing with therapy.

Discussion

This report shows that adjuvant 5-fluorouracil and levamisole can be safely administered to local patients. Toxicities, although not uncommon, resulted in 11% of patients stopping therapy. The majority of patients [245 / 341 (71.8%)] completed therapy or discontinued because of cancer recurrence. Non-haematological toxicities of therapy were mainly mild and reversible. Of the haematological toxicities, severe anaemia or thrombocytopenia was seen in only 0.7% of patients. While grade 3-4 neutropenia was present in 15% of patients, only 1 treatment-related mortality was seen.

Median recurrence-free survival was 81 months. As expected, the sites of initial recurrence were mainly the liver and lungs. At 5 years, overall survival was greater

than 60%. This is similar to results published in other studies.[2,4,5] This represents improvement in survival for patients with Dukes' C colon cancer compared to historical results which often quote 5-year survivals of approximately 35% to 50%.[1]

Preoperative CEA was available for 201 patients and was elevated in 130/341 (64.6%) of them. Elevated preoperative CEA has been shown to be a factor for predicting poorer recurrence-free survival.[6] In our patients elevated preoperative CEA was not found to be a prognostic determinant for recurrence and survival. As in other studies, the number of lymph nodes involved by metastases was an important predictor both for recurrence and survival.

A number of large scale randomised studies have demonstrated that chemotherapy offers a small but significant benefit in certain subsets of patients. Benefit has been claimed for single-agent 5-fluorouracil,[7] 5-fluorouracil + levamisole,[2] and a year of 5-fluorouracil + leucovorin.[8] Following publication of Moertel's data,[3] 5-fluorouracil + levamisole was the subject of a clinical alert from the National Cancer Institute in the United States of America and led to the rapid acceptance of this regimen as standard adjuvant therapy for this disease.

Levamisole has a fascinating history. It is an antihelminthic agent used in treating worm infestation in farm animals. Single-agent levamisole appears to have no anti-tumour activity.[3,9] Some animal model studies of levamisole as a surgical adjuvant for colorectal carcinoma showed strongly positive results,[10,11] whereas others showed decisively negative results.[12] Modulation of immunity has been the presumed mechanism for the antineoplastic activity of levamisole.[13,14]

The "best" regimen to use for adjuvant therapy of colon is debatable. Moertel et al[3] was the first to show benefit from one year of 5-fluorouracil + levamisole when compared to no adjuvant therapy. Wolmark et al[8] showed that one year of chemotherapy with 5-fluorouracil + leucovorin was beneficial compared to no adjuvant chemotherapy. One year of 5-fluorouracil + levamisole compared to one year of 5-fluorouracil + leucovorin in patients with Dukes' B2 and C colon cancer has not shown significant difference in relapse-free survival between the two arms.[15] It would appear that one year of 5-fluorouracil + levamisole is as effective as one year of 5-fluorouracil + leucovorin.

The optimal duration of chemotherapy is also being investigated. NSABP reported that 36 weeks of 5-fluorouracil + high-dose leucovorin or 36 weeks of 5-fluorouracil + high-dose leucovorin + one year of levamisole was as effective as one year of 5-fluorouracil + levamisole.[16] Another study compared 6 months of 5-fluorouracil + levamisole with 12 months of 5-fluorouracil + levamisole with 6 months of 5-fluorouracil + low-dose leucovorin + levamisole with 12 months of 5-fluorouracil + low-dose leucovorin + levamisole.[17] Six months of chemotherapy with 3 drugs was associated with the best survival but was not significantly superior to either 5-fluorouracil + levamisole for 12 months or the 3-drug combination for 12 months. Recently, a 6-month regimen of 5-fluorouracil + low-dose leucovorin was also shown to significantly reduce cancer recurrence and improve overall survival compared to no adjuvant therapy.[18] It would appear that 6 months of adjuvant chemotherapy is adequate.

An intergroup colon cancer surgical adjuvant study conducted by ECOG, South-Western Oncology Group and Cancer and Leukemia Group B, comparing 5-fluorouracil + leucovorin to 5-fluorouracil + levamisole + leucovorin to 5-fluorouracil + levamisole to 5-fluorouracil + high-dose leucovorin is currently in the follow-up phase. This large multicentre trial may help to answer some of the questions regarding which regimen and for how long.

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