Adjuvant Chemotherapy for Colorectal Cancer: A Malaysian Experience

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Summary

This study aims to evaluate the practice of adjuvant chemotherapy in colorectal cancer at the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur. A retrospective analysis of 320 patients' records from 1986 to 1994 was carried out. Adjuvant chemotherapy was given to 98 patients. Cancers of the rectum and sigmoid colon constituted over 60% of the patients. All the regimes used were 5-fluorouracil-based. The oral route was the most commonly used (55.1%). Toxicity was seldom the reason for stopping treatment (2%). The adjuvant treatment employed has been tolerable while the survival was comparable with other centres.

Key Words: Adjuvant therapy, Colorectal cancer, Chemotherapy, Toxicity, Survival, Recurrence

Introduction

Interest in the possible benefits of adjuvant therapy in colorectal cancer was stimulated largely by an appreciation that almost 50% of such patients will ultimately die of their disease despite state of the art surgery[1]. It is now generally accepted that adjuvant therapy has an important role in the management of patients with colorectal cancer, as shown in several recent studies and overviews [2-9].

Colorectal cancer is a common solid tumour in Malaysia. Cancer of the rectum is the among the top four cancers in Malays, Chinese and Indian males[10]. Patients with colorectal cancers comprised 7 per cent of new cases seen in 1992 at the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur which is the national referral centre for cancer treatment[11]. Adjuvant treatment for colorectal cancer has been carried out in this institute for at least 9 years, with a change in the protocols in line with change in current practice. Adjuvant chemotherapy has been generally employed in patients with Dukes' B and C colorectal cancer. The management is guided by the surgical and pathological findings, operation notes as well as the clinical picture at the patient's visit to our clinic. This paper serves as an audit of adjuvant chemotherapy employed whilst highlighting the toxicities and problems encountered in their use.

Materials and Methods

The records of 320 patients with colorectal cancer treated at the Institute of Radiotherapy and Oncology, Hospital Kuala Lumpur were reviewed retrospectively. The study population was patients presenting as new cases of colorectal cancer and who had undergone treatment in this Institute between 1986 and 1994.

The sample included all patients who met the following inclusion criteria: any primary malignant tumour arising for the colon or rectum (between the ileo-caecal junction and the anorectal junction), and histologically verified by a pathologist. The patient may be with or without history of other malignancies. The exclusion criteria applied in this study were: patients with primary anal cancers, metastatic cancers with unknown primary sites of disease, no histological verification, and patients whose records could not be traced.

Data was collected using a check-list questionnaire. Case notes, referral letters, histopathology reports, laboratory tests, operation findings, radiotherapy records, simulator films and other relevant investigations were reviewed. The records were retrieved manually, using the annual list of patients with various cancers compiled by staff of the Radiotherapy Clinic. Patients whose records could not be traced, and hence excluded from this analysis, were usually those treated many years ago. Otherwise, there did not appear to be any other selection bias in excluding them. Information on chemotherapy, radiotherapy treatment and complications of treatment was retrieved from the case notes. Staging of colorectal cancer was based on the Dukes' Classification[12] (Appendix 1). Chemotherapy toxicities were graded according to recommendations by the World Health Organization[13]. Marrow suppression that was recorded in this study reflected the most severe of the toxicities encountered among the various cell lines. Performance status of patients on presentation to the Radiotherapy Clinic was based on the Zubrod Scale[14].

Crude survival time was calculated from the date of primary surgery to the date of last follow-up or to the date of death due to any cause. Relapse-free interval was calculated from the date of primary surgery to the date of first relapse. Patients who had macroscopic residual disease post-operatively were considered to have no disease-free interval. Patients who were lost to follow-up had their vital status verified by sending their National Registration Identification Card Numbers to the Malaysian National Registration Department. Only the date of notification of death was furnished by the above office if the patient had died, but it was usually close to the actual date of death. The status of 16 patients are still unknown as their identification card numbers were not traceable from our records or they were from areas other than Peninsular Malaysia. Data was entered into a database management programme (DBASE IV) and analysed using EPID INFO Version 5. The follow-up of outstation patients at peripheral cancer clinics organized by the Institute had helped to update the information on these patients.

Results

Out of a total of 320 colorectal cancer cases studied between 1986 and 1994, adjuvant chemotherapy was given in 98 patients, out of whom 61 patients received adjuvant chemotherapy alone while 37 patients had combined adjuvant radiotherapy and adjuvant chemotherapy. Combined radiotherapy and chemotherapy was used in patients with tumours of the rectum (22 patients), rectosigmoid colon (5 patients), sigmoid colon (9 patients) and descending colon (1 patient). The proportion of patients with Dukes' B and Dukes' C disease who received adjuvant chemotherapy was 49.4% and 43.4% respectively.

The mean age at presentation of the patients who received adjuvant chemotherapy was 54.7 years, (s.d.= 12.5 years), with a median of 56.0 years and a range of 13 years to 78 years. Chinese comprised the largest racial group. The male:female ratio was 1.4:1. Cancers of the rectum and sigmoid colon together contributed to over 60% of all patients. Dukes' C patients were most frequently treated with adjuvant chemotherapy (46.9%), followed closely by Dukes' B (42.9%). Over

Appendix 1

STAGE	DEFINITION
A	Malignancy limited to wall with no extension into surrounding tissues
B	Malignancy has spread by direct continuity to adjacent tissues but not to nodes
C	Metastases present in regional lymph nodes
Disseminated	Distant metastases present

ninety per cent of the patients were of good performance status (Zubrod scale 0 -1) (Table I).

Table I
Demographic profile of patients

	No. of patients	
Age		
10-29	5	(5.1%)
30-49	23	(23.4%)
50-69	60	(61.2%)
70 and above	10	(10.2%)
Race		
Malay	26	(26.6%)
Chinese	64	(65.3%)
Indian	6	(6.1%)
Others	2	(2.0%)
Site of primary cancer		
Rectum	33	(33.7%)
rectosigmoid colon	12	(12.2%)
sigmoid colon	16	(16.3%)
ascending colon	9	(9.2%)
transverse colon	8	(8.2%)
descending colon	13	(13.3%)
caecum	7	(7.1%)
Dukes' stage		
A	2	(2.0%)
B	42	(42.9%)
C	46	(46.9%)
Disseminated disease	0	(0%)
Unrecorded	8	(8.2%)
Performance status (Zubrod scale)		
0	54	(55.1%)
1	36	(36.7%)
2	4	(4.1%)
3	3	(3.1%)
4	1	(1.0%)
Unrecorded	0	(0%)

All these patients were given a 5-Fluorouracil-based regime. It was used alone in 63 patients (64.3%), and in combination with other agents in the rest. None of the patients were on Leucovorin factor. The oral route was the most commonly used (55.1%). Intravenous infilsion accounted for 24.5%. The dose intensity in milligrams of 5-fluorouracil per month varied from 340 mg to 8400mg.

Adjuvant chemotherapy was commenced within 2 months of the primary surgery in 59.4%. Twenty two percent received the drug for 12 months. Twenty-nine per cent of the patients did not go beyond 6 months, either due to defaulting of treatment, progressive disease or toxicity. Thirly-two per cent of patients continued to receive adjuvant chemotherapy beyond a year.

Death is known to have occurred in 16 (16.3%) of the patients receiving adjuvant chemotherapy (Table II). The mean survival time was 26.1 months (s.d. = 20.6 months), the median survival was 20 months and the range was from 2 to 112 months. The average survival time was 5.6 years for the patients who are known to have died. The proportion of patients who are dead at the time of writing this paper in the Dukes' B and Dukes' C were 11.9% and 17.4% respectively.

Seventy five per cent of the patients have remained free of relapse (Table III). Local recurrence at the sole manifestation of relapse developed in 5%. Eighteen per cent have manifested some form of distant metastases, most commonly in the liver (13.3%). The lung was the sole site of recurrence in only one patient. The

Table II
Survival status of patients on adjuvant chemotherapy

Survival status	Number	(%)
Alive	79	(80.6%)
Dead	16	(16.3%)
Unknown	3	(3.1%)
Total	98	(100%)

mean disease free interval was 19.7 months (s.d. = 17.0 months) with a median of 16 months and a range of 0 to 112 months. A comparison between Dukes' B and Dukes' C demonstrated that the relapse free rates were 76% and 50% respectively.

The toxicity profile of the patients receiving adjuvant chemotherapy was favourable (Table IV). Diarrhoea, nausea and vomiting, mucositis, bone marrow suppression and alopecia were absent or of mild severity in the majority of the patients. The other toxicities encountered were irritant thrombophlebitis and hyperpigmentation of the skin and nails. The problem of irritant thrombophlebitis and venous access in the patients receiving infusional 5-Fluorouracil was overcome in some of the patients by the use of a totally implantable subcutaneous venous port (chemoport).

Table III
Recurrence pattern in colorectal cancer patients receiving chemotherapy

	No.	%
No recurrence	74	75.5
Local recurrence only	5	5.1
Local + distant recurrence	9	9.2
Distant recurrence only	9	9.2
Unknown	1	1.0
Total	98	100.0

The reason for stopping adjuvant chemotherapy was seldom due to toxicity of the treatment (2%). One patient had to stop the 5-Fluorouracil due to diarrhoea. Another patient stopped the chemotherapy due to generalised pruritic rash. In contrast, progressive disease and defaulting of treatment together accounted for nearly a quarter of the patients who stopped their chemotherapy (Table V).

Among the group of 37 patients who received the combination of adjuvant radiotherapy and adjuvant chemotherapy, treatment was stopped in 6 patients due to defaulting of treatment and in 4 patients due to progressive disease.

Discussion

The proportion of patients with colorectal cancer who received adjuvant therapy was similar to Singapore figures wherein 31% of their patients received adjuvant post-operative adjuvant therapy[15]. The decision to commence adjuvant chemotherapy was influenced by the stage at which patients presented to the Institute and its practicability in each patient. The low proportion of patients with Dukes' stage B and C disease who received adjuvant chemotherapy could also be explained by the fact that the benefits of adjuvant

Table IV
Toxicity of adjuvant chemotherapy (n=98)

	Chemotherapy toxicity			
	Grade 0 No. (%)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)
Diarrhoea	75 (76.5)	6 (6.1)	4 (4.1)	1 (1.0)
Nausea/vomiting	83 (84.7)	2 (2.0)	1 (1.0)	0
Mucositis	82 (83.7)	2 (2.0)	2 (2.0)	0
Marrow suppression	79 (80 6)	4 (4.1)	3 (3.1)	0
Alopecia	83 (84.7)	2 (2.0)	1 (1.0)	0

The toxicity was unrecorded in the remaining patients.

Table V
Reason for stopping adjuvant chemotherapy

Chemotherapy status	No. of patients	%
Continuing chemotherapy	39	40.0
Completed chemotherapy	29	30.0
Progressive disease	12	12.0
Defaulted treatment	11	11.0
Toxicity	2	2.0
Unknown	5	5.0
Total	98	100.0

chemotherapy for colorectal cancer had not been established prior to 1990.

It is interesting to note that the Chinese form the largest racial group which is dissimilar to that of the racial composition in this country. Several possible explanations include their dietary habits, their genetic susceptibility or their tendency to seek medical attention more readily. The relatively young age of patients with colorectal cancer at presentation has been demonstrated in this study. In comparison, persons under age 40 constituted only 2.5% of colorectal malignancies in Sweden[16].

Evidence is accumulating that adjuvant therapy delays or prevents the recurrence of the tumour and improves survival by eliminating presumed micrometastases. An overview[2] of published randomised controlled trials of adjuvant therapy of colorectal cancer showed that fluorouracil-containing regimens resulted in a modest benefit of therapy in terms of overall survival.

This institute has used 5-fluorouracil as the mainstay of adjuvant therapy and neither MeCCNU (semustine) nor folinic acid has been adopted in its regimens. Levamisole was added based on results obtained by the NCCTG/Mayo study[6] and the Intergroup study[7] which suggested benefits in disease free survival and overall survival in the patients given the combination of 5-fluorouracil and levamisole. Protracted 5-Fluorouracil infusion in the treatment of rectal carcinoma has been shown to be superior to bolus injections when time to tumour recurrence and tumour control were compared[17]. Omission of MeCCNU (Semustine) which had been a component of earlier regimes of adjuvant chemotherapy did not appear to have a detrimental effect on overall survival or recurrence rates[18]. Some papers have suggested that the addition of folinic acid to 5-fluorouracil reduced the recurrence rate when used in the adjuvant setting[8,19] but the benefits of this combination need to be confirmed by larger studies with a longer follow-up.

Of all the patients in our group who received adjuvant chemotherapy, 24% have developed a recurrence, with a median disease free interval of 16 months. By comparison, 46% of the patients in the Gastrointestinal Tumor Study Group[3] developed a recurrence; the median time to recurrence in the control arm was 31 months.

Several trials have suggested that combined chemotherapy and radiotherapy as adjuvant treatment in patients with rectal cancer reduce both the local and distant recurrence of rectal cancer. In addition, benefit has also been seen in cancer-related deaths and the overall death rate. Unfortunately, the incidence of severe and delayed treatment-related morbidity in patients receiving combined modality treatment was also higher. In the combined modality arm of the GITSG study[3], haematologic toxicity in which the white cell count was less than 2,000 per cubic millimeter occurred in 26% while severe non haematologic toxicity was present in another 35%. The chemotherapy had to be stopped prematurely in approximately a third of patients receiving combined radiotherapy and chemotherapy in this trial because of acute toxicity. In contrast, patients in our centre undergoing combination adjuvant pelvic radiotherapy plus chemotherapy seldom experienced severe toxicity. The main reason for stopping therapy in our series was progressive disease whilst toxicity accounted for only 2%.

An analysis of crude survival is more realistic than disease-specific survival, especially in Malaysia where certification of death is often made by non-medical personnel and postmortems are rarely carried out. In this study, average crude survival time of 5.6 years for

patients who are known to have died in the adjuvant chemotherapy group appear to be similar to GITSG trial[3] in which the median time between surgery and the date that a patient was last known to be alive was 59 months. Although the subset of patients most likely to benefit from adjuvant therapy are those in Dukes' stage C[9], 40% of patients in our study were in Dukes' B. This is due to the relative lack of toxicity of adjuvant therapy in our centre and hence the policy to treat has been extended to patients in Dukes' stage B.

In conclusion, the toxicity of the adjuvant treatment employed in our centre has been relatively modest and therefore tolerable. This is an extremely important consideration in adjuvant treatment. Despite the fact that the oral route of chemotherapy had been extensively used in our centre, our results for survival appear to be comparable with published data. However, caution must be exercised when crude survival is compared with disease-specific survival rates reported in other studies.

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