AJMS
(A US National Library of Medicine enlisted journal)
Al Ameen J Med Sci (2012)5(2):116-123
ISSN 0974-1143
CODEN: AAJMBG

ORIGINAL ARTICLE

Evolution of Adjuvant Chemotherapy and Efficacy of Commonly Used Regimens in Colorectal Cancer

S.M. Adiga[1], K. Meena Kumari[2], K.L. Bairy[2*], M. Amberkar[2], B.M.Vadiraja[3] and M.S.Vidyasagar[3]

[1]Department of Pharmacology, Indira Gandhi Medical College & Research Institute, Puducherry, India, [2]Department of Pharmacology, Kasturba Medical College, Manipal, Karnataka, India and [3]Department of Oncology & Radiotherapy, Kasturba Medical College, Manipal, Karnataka, India

Abstract: *Objective:* to know the evolution of adjuvant chemotherapy treatment given and to evaluate the efficacy of two commonly used regimens. *Background:* Colorectal cancer in Indian population is on upward swing due to the change in dietary habits and many other factors. The treatment of colorectal cancer has changed drastically over a period of time. *Method:* Patients diagnosed of this cancer and treated with adjuvant chemotherapy from 1997 to 2006 in our hospital were included for the study. Patients treated from 1997-2001 were followed up for a period of five years. The efficacy of two regimens were analyzed by five year overall survival rates in the respective group. *Results:* 5–fluorouracil monotherapy and 5-fluorouracil with levamisole were the commonly used regimens during 1997 - 2001 whereas in the later half, 5-fluorouracil+ leucovorin was the commonest regimen. Five year overall survival was 46% & 20% in stage B & C in 5- fluorouracil + levamisole group whereas it was 36% and 10 % respectively in 5- fluorouracil monotherapy group. *Conclusion:* We conclude from our findings that 5- fluorouracil+ levamisole regimen had better five year overall survival than 5-fluorouracil.

Keywords: Adjuvant chemotherapy, Overall survival, 5-fluorouracil, 5-fluorouracil+ levamisole

Introduction

Among all cancers, colorectal cancer accounts for 10-15% and this is the second leading cause of cancer death in western countries [1]. Due to various reasons, the incidence of colorectal carcinoma is on raising increasing trend in India [2]. In Indian population, it's incidence in males and females is 6.7: 5.5 per 100000 populations respectively. Dietary habits, familial adenomatous polyposis and various others epidemiological factors are the risk factors for this cancer [3]. Surgery is the primary modality of treatment and it varies according to the site of tumor. Systemic chemotherapy plays a major role in various stages of colorectal cancer. Chemotherapy and radiotherapy have a clear role in adjuvant therapy and for symptom palliation in advanced disease [4]. 5- fluorouracil(5-FU) based regimens forms the main adjuvant chemotherapy in which levamisole (lev), leucovorin(LV), oxaliplatin, capecitabine, irinotecan are used along with it. The treatment of colorectal cancer has witnessed constant evolution over the past two decades with every regime has its own advantage and disadvantage. Great number of deaths occur each year from the disease as well as due to the adverse effect of anticancer drugs.

There are sufficient data regarding the efficacy of various regimens used in different stages of colorectal carcinoma among western population. The risk factors in our patient population is different from the risk factors in western population, hence the efficacy. To best of our knowledge there is lack of data about the efficacy of different regimens in Indian patient population. Hence a study was planned to know the evolution of adjuvant chemotherapy in colorectal cancer during 1997-2006 and to evaluate the efficacy of different chemotherapeutic regimens used in our hospital set up during 1997-2001.

Material and Methods

In this retrospective study, patients of either sex, diagnosed to have colorectal cancer of stage B or C by histopathology were included. The study was conducted in Shri Shiridi Sai Saba Cancer Institute, Manipal (A wing of Kasturba Hospital, Manipal, India) which is a referral hospital for South Karnataka, neighbouring states such as Goa and northern districts of Kerala, The study was approved by the Kasturba Hospital Ethics Committeee.The data of colorectal cancer patients diagnosed and treated from 1997 to 2006 was collected. The necessary information such as staging of cancer (modified Astler –Coller Dukes' system), type of adjuvant chemotherapy received were collected from the hospital medical records for each patient. The status of the patient (doing well, expired) after receiving chemotherapy was enquired by writing self-addressed post card to the patient and patient's attenders, if it was not available in case sheet. Efficacy was evaluated by using five year overall survival (From time of diagnosis to time the last follow up / death, in months) for the commonly used regimens such as 5-fluorouracil alone (5- FU) and 5-FU + levamisole (5-FU+lev) as this regimen was commonly used in our hospital set up between 1997-2001.

Statistical Analysis: Five year overall survival, in various stages (B& C) as well as for various chemotherapeutic regimens(5-FU, 5-FU+lev) were calculated by using survival curves, which plot percent survival as a function of time using the method of Kaplan and Meier (Graph-pad Prism statistical software package). The percentage of survival were obtained by drawing a perpendicular line from X axis at the interval of 60 months (5 years) to the curve and drawing a horizontal line from that point to Y axis which denotes the survival in years.

Results

In this study we have analyzed the data of 304 patients of colorectal cancer, who were treated during 1997-2006.The patient demographic profiles were given in table 1.

There were more than twenty chemotherapeutic regimens used for the treatment of colorectal cancer in the past decade (1997-2006) in our hospital. Among them, 5-FU alone (36.18%) was the commonest regimen followed by 5-FU+LV combination (28.61%) and 5-FU+ lev combination (19.41%) (table 2).

Table-1: Showing patient characteristics (values in parentheses denotes percentage)		
Patient characteristics		Number
Total number of patients		304
Male to female ratio		199:105 (65.46:34.54)
Age distribution (In years)	31-40	48 (15.79)
	41-50	59 (19.42)
	51-60	93 (30.59)
	61-70	62 (20.39)
	Miscellaneous	42 (14.81)
Patients in different stages	B	180 (59.21)
	C	110 (36.18)
	D	14 (4.61)
Patients completed one regimen	B	62 (34.44)
	C	29 (26.36)

Table 2: The chemotherapeutic regimens used during 1997-2006 for colorectal cancer

Chemo regimen	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Total (cases)
5-FU	20	17	5	9	9	18	9	14	5	4	110 (36.18%)
5-FU+lev+CCNU	3	1	-	-	-	-	-	-	-	-	04
5-FU+lev	5	6	12	15	8	5	2	-	4	2	59 (19.41%)
5-FU+ CCNU	4	-	1	-	-	-	-	-	-	-	5
5-FU+LV	1	-	3	1	4	11	15	11	22	19	87 (28.61%)
MT	1	-	-	-	-	1	-	-	-	-	02
CP	-	1	-	-	-	-	-	-	-	-	01
CP+5-FU	-	1	-	-	-	-	-	-	-	-	01
5-FU+ CCNU+AD	-	1	-	-	-	-	-	-	-	-	01
5-FU+ AD	-	-	1	-	-	-	-	-	-	-	01
5-FU+MT +DOX	-	1	-	-	-	-	-	-	-	-	01
IR	-	-	1	-	-	-	-	-	-	-	01
CIS	-	-	1	-	-	1	-	-	1	-	03
5-FU+ CIS	-	-	-	-	1	1	-	-	1	1	04
CAP	-	-	-	-	-	1	1	2	-	1	05
OXP	-	-	-	-	-	1	1	1	4	3	10
5FU+LV+OXP	-	-	-	-	-	-	-	-	1	1	02
OXP+CAP	-	-	-	-	-	-	-	-	-	1	01
LV+FUDR	-	-	-	-	-	1	1	-	-	-	02
5-FU+lev+LV	-	-	-	-	-	-	1	-	-	-	01
AD+MT	-	-	-	-	-	-	-	-	-	1	01
5-FU+MT	-	-	-	-	-	-	-	2	-	-	02
Total	34	28	24	25	22	40	30	30	38	33	304

5-FU- 5 Fluorouracil, lev-Levamisole, LV- Leucovorin, AD- Adriamycin, MT- Mitomycin DOX- Doxorubicin, OXP- Oxaliplatin, CAP- Capacitabine,CCNU-Lomustine, CP-Cyclophosphomide, FUDR- Fluoxiuridine,CIS-Cisplatin,IR- Irinotecan

Table-3: The preference of chemotherapeutic regimens during 1997-2006 for colorectal cancer (Values in parentheses denotes percentage).

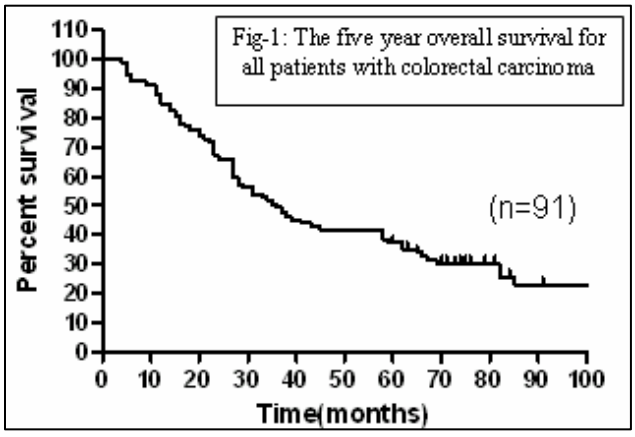
Regimen	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	
5-FU	20 (38.82)	17 60.71)	5 20.83)	9 (36)	9 (49.90)	18 (45)	9 (33.3)	14 (46.6)	5 (13.15	4 (12.1)	110
5FU+lev	5(14.7)	6(21.42)	12(50)	15 (60)	8 (36.36)	5	2	0	4	2	59
5FU+LV	1	0	3	1	4	11 (27.5)	15 (30)	11 (36.6)	22 (57.9)	19 (57.57)	87

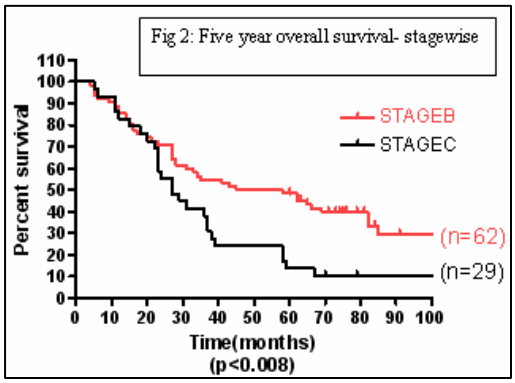
5-FU- 5 Fluorouracil, lev-Levamisole, LV- Leucovorin

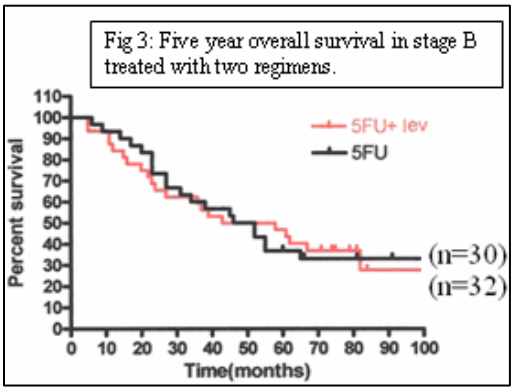
This was 48 % in stage B and 15% in stage C (fig 2). Stage B and C patients had a statistically significant different 5 year overall survival rates ($p<0.008$). The overall survival in 5-FU treated group of stage B was 36% at 5 years.

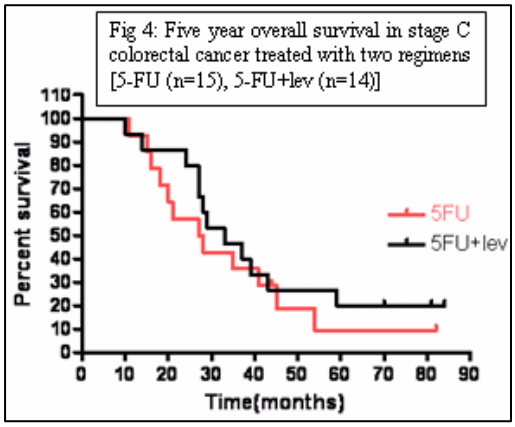
Evolution of chemotherapy in the treatment of colorectal cancer: In the initial two years of our study period (1997-1998), 5-FU was the common regimen used (58.82 % & 60.71%) followed by 5-FU + lev (14.70% & 21.42%). In the next two years i.e. from 1999-2000, 5-FU+lev (50% & 60%) was the commonly used regimen followed by 5-FU monotherapy and 5-FU+LV. In the next five years the preference has clearly shifted to 5-FU+LV regimen and 5-FU continues to be the other common regimen (table 3). 5-FU + levamisole regimen has slowly disappeared from treatment protocol and newer regimens like oxaliplatin, capecitabine were used as sole agents in advanced colorectal carcinoma from 2002 (table 2). The number of regimens used during this period obviously indicates the constant evolution in the treatment with an eye over improving the efficacy always.

Efficacy of different chemotherapeutic regimens: Even though we have collected the data of ten years, we analyzed the data of patients who have been treated in our hospital for colorectal carcinoma during 1997-2001.Five year overall survival was calculated and expressed in percentage. The five year overall survival in our patient population (all patients) was 37% (fig 1).









The survival with 5-FU + lev combination was 46% at five years. There was no statistical significant difference between the two treatment groups (figure 3). The overall five year survival in stage C of patients treated with combination of 5-FU + lev was 20%. This was 10% in patients treated 5-FU alone (figure 4).

Discussion

Since the adjuvant therapy has not yet proved to offer better survival, patients with stage II colon cancer (Dukes B) were encouraged to participate in the on-going trials [5-6]. The use of adjuvant chemotherapy had increased the likelihood of cure by 30% among patients with stage III [7] which is also called as Dukes C stage. In the early part of last decade 5-FU + lev (levamisole) combination was used as the principle adjuvant chemotherapy regime for colon cancer of Stage III. Post operative 5-FU based chemotherapy combined with irradiation should be the standard clinical approach for stage II and stage III for rectal cancer since this approach had shown to decrease in local recurrence, cancer related deaths and overall mortality [8]. Staging of the cancer, other treatment modalities received, the tolerability and affordability for a particular regimen are some of the factors which decides the selection of an adjuvant chemotherapeutic regimen in a given set up. A lot of progress has taken place in the management of colorectal cancer in the past two decades hence the study was conducted to know the evolution of colorectal cancer in our set-up.

5-FU was used as the sole agent in significant number of patients during 1997 and 1998 in our set-up. Although the use of 5-FU had decreased after 1999, this continued to be one of the common regimens during the entire period (till 2006).

5-fluorouracil along with levamisole was the other adjuvant chemotherapy, which was most commonly used during 1999-2001 period (table 3). After this period (from the year 2002 onwards), 5-FU based leucovorin therapy remained as the principle adjuvant chemotherapeutic regimen for colorectal cancer patients treated in our hospital. The paradigm shift in the preference could be due to the fact that by 1998, 5-FU+LV was considered superior to 5-FU+lev [9]. Apart from the above three treatment regimes, other 5-FU based regimes were used between 1997-2001 were 5-FU + lomustine (CCNU), 5-FU + lev + CCNU, 5-FU + Adriamycin, 5-FU + cyclophosphamide, 5-FU + Mitomycin which have become almost obsolete during this time. Hence we could see very few patients receiving this regimen among our patient population. During the latter half of our study (2002-2006); oxaliplatin, capecitabine, 5-FU + cisplatin, leu + 5-FU + oxaliplatin, oxaliplatin +capecitabine, were the other adjuvant chemotherapeutic regimes used for treatment of colorectal cancer, apart from the commonly used regimens. During this time, the adjuvant chemotherapy has seen a remarkable change. Irinotecan, FOLFOX (5-FU, LV & oxaliplatin), oxaliplatin and irinotecan combinations have come the management of colorectal cancer [10-12]. The treatment for colorectal cancer used to be more or less same in our patients compared to the literature available. The notable difference seen in our study was that during 1997-2001 period, 5-FU + lev was one of the common regimen used in our patients, which was rarely used in rest of the world. As evidenced during the early part of this millennium i.e. 2002-2006, Oxaliplatin and capecitabine have slowly gained importance in addition to 5-FU + LV regimen.

Adjuvant chemotherapy was regarded as the standard treatment for stage III colon cancer; however, use of chemotherapy after surgery in patients with stage II disease remains controversial because of a lack of evidence. In 2005, European Society for Medical Oncology (ESMO) did not advocate use of chemotherapy in stage II disease, but did state that chemotherapy may be considered in selected node-negative patients. Another study stated that adjuvant therapy can be given for patients with inadequately sampled nodes, T_4 lesions, and perforation of poorly differentiated histology. Hence, use of adjuvant chemotherapy in patients with stage II colon cancer is not universal [13]. We have analyzed the efficacy of two commonly employed adjuvant chemotherapeutic regimens in stage II (Dukes B) and stage III (Dukes C) colorectal cancer patients who have received treatment during 1997-2001. These patients were further followed up for five years to analyze the efficacy of a regimen in terms of five year overall survival. Efficacies of other regimens were not analyzed because of less number of cases.

According to National Surgical Adjuvant Breast and Bowel Project (NSABP) study analysis, 5-FU + lev administered for stage II colorectal cancer patients had a 5 year overall survival of 81 %. This combination has also reduced the overall death rate by 36% when compared to surgery alone or surgery and levamisole [5, 14].In our patients, 5 year overall survival was 46%, with the above combination. The reason for lesser efficacy could be due to relatively severe cases and less number of patients analyzed in that group.

For stage III colorectal cancer, the combination of 5-FU + lev given for one year following surgery was the first regimen to be unequivocally associated with a survival benefit. This drug combination was recommended in clinical practice by a National Institute of Health Consensus Development Conference, for patients with stage III (Duke's C) colon cancer in 1990 [15]. In NSABP study, similar treatment had a five year overall survival of 63% [4]. However the overall survival rate in our patient treated with 5-FU+ lev was 20%. There is little confusion over the use of 5–FU monotherapy in stage II colorectal cancer. But one randomized clinical trial had revealed that the five year overall survival was 55.6% in stage III [16]. Our study had shown a five year overall survival of 10% in stage III. Hence we conclude that the overall survival rates with all the regimens were significantly less in our population when compared to the standard literature available. The combination of 5-FU + lev had a slight edge over 5-FU alone in both stages of colorectal cancer.

Acknowledgements

We are grateful for the patients and relatives for giving cooperation and valuable data, medical superintendent of Kasturba Hospital Manipal for the access of data and staff of medical record department, Kasturba Hospital.

References

1. Bleiberg Harry. Adjuvant treatment of colon cancer. *Current Opinion in Oncology* 2005; 17(4): 381-385.
2. Mohandas KM, Desai DC. Epidemiology of digestive tract cancers in India. V. Large and small bowel. *Indian J Gastroenterol* 1999; 18:118–121.
3. Libuti SK, Saltz LB, Rustgi AK, Epper JE. In: Devita VT Jr, Hellman S, Rosenberg SA. In Cancer: Principles and practice of oncology. 7th edn. Philadelphia: *Lippincott Williams and Wilkins,* 2005; 1061-1062.
4. Terashima M, Hoshino Y, Gotoh M. Comparisons of standard treatments for colorectal cancer between Japan and Western Countries. *Cancer and chemotherapy,* 2007; 34(5):694-9.
5. Mamounas E, Wieand E, Wolmark N et al. Comparative efficacy of adjuvant I chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: Results from four National Surgical Adjuvant Breast and Bowel Project Adjuvant studies (C-01, C-02, C-03 and C-04). *J Clin Oncol* 1999; 17: 1349- 1355.
6. Bigas MAR, Lin EH, Crane CH. Adenocarcinoma of colon and rectum. In: Kufe DW, Pollock RE, 6th eds. Cancer medicine. London: *BC Decker Inc.* 2003; 1635-1665.
7. Moertel CG, Fleming TR, MacDonald JS, Haller DG, Laurie JA, Goodman PJ et al. Levamisole and Fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; 322: 352-8.
8. NIH Consensus Conference Adjuvant therapy for patients with colon and rectal cancers. *JAMA* 1990; 264: 1444-1450.
9. Kopetz S, Freitas D, Calabrich AFC, Hoff PM. Continuing medical education on Adjuvant Chemotherapy for Stage II colorectal cancer. *Oncology*, 2008; 22(3): 260-270
10. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ et al.Irinotecan plus fluorouracil for metastatic colorectal cancer. *New Engl J Med* 2000; 343:905-914.

11. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J et al. Leucovorin and fluorouracil with or without oxaliplatin as the first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938-47.
12. Goldberg RM, Mortan D, Sargent J. N9741: Oxaliplatin or CPT 11 plus 5 Fluorouracil/Leucovorin (LV) or oxaliplatin + CPT 11 in advanced colorectal cancer (CRC), Initial toxicity and response data from a GI Intergroup study. *Proc Am Soc Clin Oncol* 2002; 21:A511.
13. Sobrero A. Should adjuvant chemotherapy became standard treatment for patients with stage II colon cancer for the proposal. *Lancet Oncol* 2006; 6: 516-17.
14. Laurie JA, Moertel CG, Fleming TR et al. Surgical adjuvant therapy of large bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil: The North Central Cancer Treatment Group and the Mayo Clinic. *J Clin Oncol* 1989; 7:1444-56.
15. O'Connell MJ, Laurie JA, Kahn M, Fitzgibbons RJ, Erlichman JR C, Shepherd L et al. Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. *J Clin Oncol* 1998; 16(1): 295-300.
16. Iwashyna TJ, Lamont EB. Effectiveness of adjuvant fluorouracil in clinical practice: A population based cohort study of elderly patient with stage III colon cancer. *J Clin Oncol.* 2002; 20(19):3992-8

*All correspondences to: Dr. K.L. Bairy, MD, PhD. Professor of Pharmacology, Kasturba Medical College, Manipal-576104, Karnataka, India, Email: klbairy@yahoo.com