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ORIGINAL ARTICLE

Adjuvant chemotherapy outcomes in patients over 65 years with early stage colorectal carcinoma

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Summary

Purpose: *To evaluate the clinicopathological characteristics and the outcomes of adjuvant chemotherapy of patients with colorectal cancer aged ≥65 years.*

Methods: *Between March 2003 and December 2010, the medical files of 562 colorectal cancer patients ≥65 years of age who were under follow-up in Ankara Numune Educational Hospital, Department of Medical Oncology, were retrospectively analyzed. Only 210 patients with non-metastatic disease at the time of diagnosis and those who had undergone surgical resection were included in the study.*

Results: *The patient median age was 71 years (range 65-87). Of the patients, 115 (54.8%) were males and 95 (45.2%) females. The most common involvement site was the rectum (41.4%), followed by sigmoid colon (21.9%). According to the TNM staging, 12.4% patients had stage I, 48.6% stage II, and 39% stage III disease. At the time of diagnosis 19 patients (9%) had ECOG PS 0, 112 (53.3%) ECOG PS 1, 61 (29%) ECOG PS 2, and 16 (7.7%) ECOG PS 3. Of the patients, 141 (66.5%) were administered adjuvant chemotherapy, whereas 69 patients (33%) were not. Thirty nine (18.6%) patients with adjuvant chemotherapy received fluorouracil/folinic acid (FUFA) weekly, 59 (28%) received FUFA infusion, and 43 (21%) received oxaliplatin, folinic acid and 5-fluorouracil (FOLFOX-4) regimen. The median follow-up was 27 months (range 1-116). Disease free survival (DFS) was not reached during the follow-up period. The estimated overall survival (OS) was 68.8 months (range 48.5-73.0). Sixty six (31%) patients died during follow-up.*

Conclusion: *Elderly patients with high risk for recurrence of colorectal cancer must receive adjuvant chemotherapy after curative surgery. Infusional FUFA seems more effective than other regimens.*

Key words: *adjuvant chemotherapy, colorectal cancer, elderly patients, FOLFOX-4, FUFA*

Introduction

Despite technological developments in the diagnostics and therapeutic fields in recent years, colorectal cancer remains one of the leading health problem issues [1]. Nearly 70% of all cases with colorectal cancer are at ≥65 years of age [1]. It is predicted that the number of patients who are diagnosed with colorectal cancer will be doubled by 2030, and the diagnosis of colorectal cancer will increase each passing year with the increasing aging population [2].

Although the incidence of colorectal cancer is 6-fold higher in the elderly (≥65 years) than in young adults and most of the patients have advanced disease with increased disease-related mortality, no randomized-controlled clinical study investigating the efficacy of adjuvant chemotherapy in this patient population has been carried out yet [3]. On the other hand, there are several studies including young patients or including both young and elderly patients, but reporting overall results. Meta-analyses of data related to elderly populations enrolled in clinical studies showed

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that the elderly benefited from chemotherapy similarly as young patient populations [4,5]. Most of these data have been derived from fluorouracil plus leucovorin (FU/LV) studies [4-7].

In this study, we aimed to evaluate the clinicopathological characteristics and treatment outcomes of patients with colorectal cancer being over 65 years of age.

Methods

Patient selection

Between March 2003 and December 2010, the medical files of 562 patients aged ≥65 years who were under follow-up in Ankara Numune Research and Training Hospital, Medical Oncology Clinic, with the diagnosis of colorectal carcinoma were retrospectively analyzed. Only 210 patients with non-metastatic disease at the time of diagnosis and those who had undergone surgical resection were included in the study, whose demographic and survival data were adequate.

All data were documented in the study protocol forms. The age at diagnosis, date of diagnosis, sex, complaints, localization, type of surgery, tumor grade, Eastern Cooperative Oncology Group performance status (ECOG PS), TNM stage, number of lymph nodes dissected, baseline CEA and CA19-9 level, adjuvant chemotherapy, chemotherapy regimen, recurrence during follow-up, date and localization of recurrence, systemic chemotherapy for recurrence, date of the last visit, survival status, and chemotherapy-related toxicities were recorded.

Chemotherapy

Chemotherapy regimens administered were mFOLFOX-4 (folinic acid 400mg/m^2 d1, oxaliplatin 85 mg/m^2 d1, 5-fluorouracil 400 mg/m^2 d1 iv bolus and 2400 mg/m^2 46-hr continuous infusion every two weeks for 8-12 cycles), infusional FU-FA (folinic acid 400 mg/m^2 d1, 5-fluorouracil 400 mg/m^2 d1 iv bolus and 2400 mg/m^2 46-hr continuous infusion every two weeks for 8-12 cycles), and weekly FU-FA (folinic acid 25 mg/m^2 d1, 5-fluorouracil 425 mg/m^2 d1 iv bolus weekly for 4 weeks every 6 week for 4-6 cycles)

Toxicity

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE.4.0) and dose reductions were planned by the attending physician according to the degree of toxicity severity.

Survival

OS was defined as the time from diagnosis to death or last follow-up, while DFS was defined as the time from diagnosis to the first recurrence and/or metastasis.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences v18.0 (SPSS Inc., Chicago, IL, USA). Descriptive analyses were used to estimate percentages, median, and mean values. Survival rates were estimated using the Kaplan-Meier survival analysis and log-rank test. Further factors affecting survival were studied by Cox regression analysis. A bi-directional p-value was applied in all analyses and statistical significance was set at $p<0.05$.

Results

The patient median age was 71 years (range 65-87) (Table 1). Of the patients, 115 (54.8%) were males and 95 (45.2%) females. The most common involvement site was the rectum (41.4%), followed by sigmoid colon (21.9%). Of the patients 45.7% and 24.3% were admitted with hematochesia and pain, respectively. The most frequently used surgical techniques included low anterior resection (LAR) in 43.8% and abdominoperineal resection (APR) in 24.3% of the patients. According to the TNM staging, 12.4% of the patients had stage I, 48.6% stage II, and 39% stage III disease. At the time of diagnosis, 19 patients (9%) had ECOG PS 0, 112 (53.3%) ECOG PS 1, 61 (29%) ECOG PS 2, and 16 (7.7%) ECOG PS 3. In addition, 141 patients (66.5%) were administered adjuvant chemotherapy, and 69 (33%) were not. Thirty nine (18.6%) of the patients with adjuvant chemotherapy received weekly FUFA, 59 (28%) received FUFA infusion, and 43 (21%) received oxaliplatin, folinic acid and 5-fluorouracil (FOLFOX-4). Table 1 shows patient distribution according to the treatment administered. The characteristics of the patients receiving adjuvant chemotherapy are presented in Table 2.

The patients receiving adjuvant chemotherapy were younger compared with those not receiving chemotherapy (71 vs 73 years; p=0.007). The number of patients with ECOG PS 3 was lower in the study population receiving adjuvant chemotherapy (18.6 vs 22%; p=0.001). Furthermore, the percentage of patients on adjuvant chemotherapy with rectal cancer (47 vs 30%; p=0.001) and stage III disease (52.9 vs 11.4%; p<0.0001) was significantly higher. Of note, none of the patients with stage I disease received adjuvant chemotherapy.

Table 1. Patient distribution according to disease characteristics and treatment administered

Characteristics	*Infusional FUFA N (%)*	*Weekly FUFA N (%)*	*FOLFOX-4 N (%)*	*p value*
Gender				
Male	32 (54)	19 (19)	27 (62)	0.40
Female	27 (46)	20 (20)	16 (38)	
ECOG PS				
1	40 (68)	18 (49)	35 (82)	0.04
2	17 (28)	17 (47)	8 (18)	
3	2 (4)	2 (4)	-----	
Localization				
Right colon	9 (15)	6 (15)	7 (16)	0.16
Left colon	3 (5)	1 (2)	4 (9)	
Sigmoid	8 (14)	12 (31)	11 (25)	
Rectum	35 (59)	17 (43)	14 (32)	
Rectosigmoid	4 (6)	3 (9)	7 (16)	
Surgery				
Right hemicolectomy	8 (14)	6 (15)	7 (16)	0.47
Left hemicolectomy	7 (12)	5 (13)	8 (19)	
APR	12 (20)	14 (36)	9 (21)	
LAR	30 (51)	14 (36)	19 (44)	
Stage				
I	-----	-----	-----	0.0001
II	41 (69)	22 (47)	2 (5)	
III	18 (31)	16 (53)	41 (95)	
Grade				
I	30 (50)	17 (44.7)	21 (48.8)	0.86
II	28 (48.3)	19 (50)	21 (48.8)	
III	1 (1.7)	2 (5.3)	1 (2.3)	
Basic CEA (ng/ml)				
>5	40 (72.7)	25 (69.4)	27 (64.3)	0.67
<5	15 (27.3)	11 (30.6)	15 (35.7)	

Disease-free survival data

The median follow-up was 27 months (range 1-116). DFS was not reached during the follow-up period. Fifty five (26%) patients developed recurrence or distant metastasis. There was no statistically significant impact of sex (p=0.67), PS at the time of diagnosis (p=0.44), adjuvant chemotherapy administration (p=0.74), and insufficient lymph node dissection (<12 lymph node dissection) (p=0.59) on DFS.

Stage III patients at the time of diagnosis had poor prognosis, compared to those with stage I/II (p=0.053).

Although FUFA infusion seemed to be more effective than other chemotherapy regimens, it did not reach statistical significance (p=0.14) (Figure 1). Three-year DFS rates were 76.8, 60.8 and 56.0% in patients receiving FUFA infusion, FUFA weekly, and FOLFOx-4, respectively.

Left colectomy including APR and LAR (p=0.03), presence of mucinous component (p=0.025), CEA >5 ng/mL at the time of diagnosis (p=0.002), and advanced nodal stage (p=0.009) affected adversely DFS rates.

Overall survival data

The median OS was 60.8 months (range 48.5-73.0). Sixty six (31%) patients died during follow-up. Among them 54 (25.7%) died because of disease progression and the remaining 12 due to comorbidties and other diseases. There was no statistically significant impact of sex (p=0.37), tumor grade (p=0.74), insufficient lymph node dissection (p=0.26), and adjuvant chemotherapy (p=0.38) on OS. However, there was an almost statistically significant effect of the presence of mucinous component at the time of diagnosis on OS (p=0.054) (Figure 2).

Poor PS (p=0.001), left colectomy (p=0.003), advanced disease at the time of diagnosis (p=0.0038), and advanced nodal stage irrespective of disease stage (p=0.002) suggested a statistically significant poor OS.

Toxicity

The most common adverse effect was diarrhea in patients receiving adjuvant chemotherapy. Tox-

Table 2. Basic patient, disease and chemotherapy characteristics

Characteristics	*N*	*%*
Gender		
Male	115	54.8
Female	95	45.2
Age at diagnosis (years)		
65-69	88	41.9
70-75	74	34.8
76-80	33	15.7
>80	15	7.6
Symptoms		
Hematochesia	96	45.7
Pain	51	24.3
Ileus	26	12.4
Other	37	17.6
ECOG PS		
0	19	9.1
1	114	54.4
2	61	29.3
3	16	7.2
Localization		
Rectum	87	41.4
Sigmoid	46	21.9
Rectosigmoid	24	11.4
Right colon	35	16.7
Left colon	18	8.6
TNM stage		
I	26	12.4
II	102	48.6
III	82	39.0
Differentiation		
Good	116	55.5
Moderate	88	41.6
Poor	6	2.9
Chemotherapy regimens		
No chemotherapy	69	32.9
Weekly FUFA	39	18.6
Infusional FUFA	59	28.0
FOLFOX	43	20.5
Recurrence		
Yes	57	29.2
No	138	70.8
Outcome		
Alive	127	65.5
Dead	67	34.5

icity profile is shown in Table 3. A total of 2.8% patients received primary prophylaxis for leukopenia with granulocyte-colony stimulating factor (G-CSF).

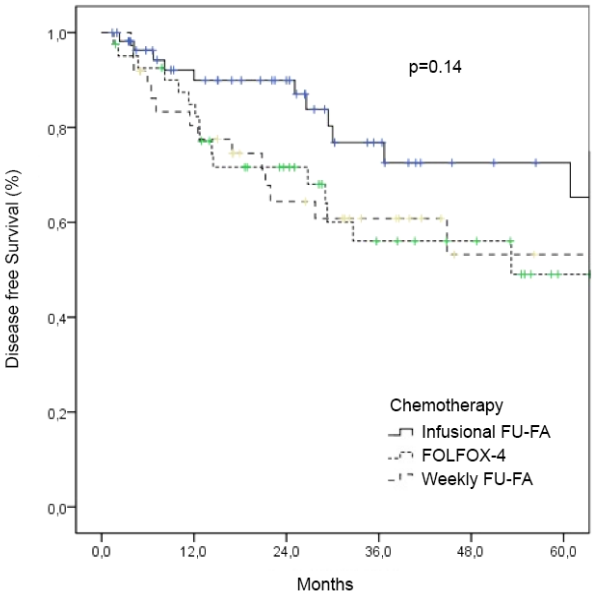

Figure 1. Disease free survival according to chemotherapy regimen

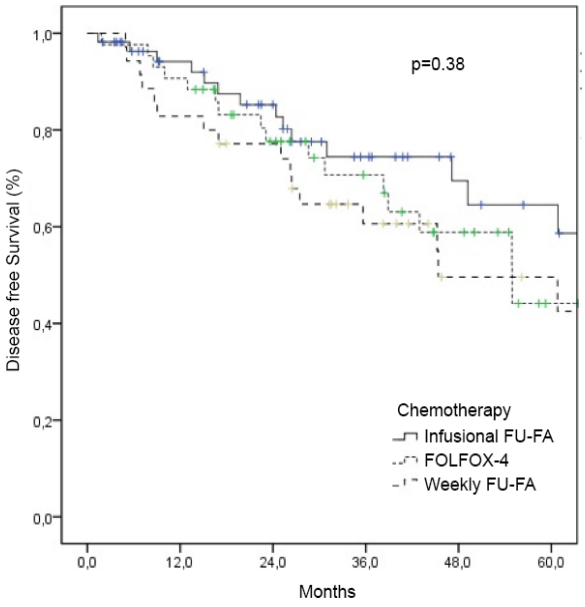

Figure 2. Overall survival according to chemotherapy regimen.

Discussion

Several studies have shown that adjuvant chemotherapy has a considerably beneficial effect on recurrence and survival in most patients with colorectal cancer [8-15]. However, there is limited evidence on the use of adjuvant chemotherapy in patients ≥65 years of age. Although the patients receiving adjuvant chemotherapy had worse clinicopathological characteristics and prognosis in our study, the survival rates were similar to those with good prognosis who did not receive adjuvant

Table 3. Toxicity according to treatment administered

Toxicity	*Infusional FUFA N (%)*	*Weekly FUFA N (%)*	*FOLFOX-4 N (%)*
Dose reduction	1 (1.5)	2 (5.1)	5 (11.6)
Cycle delay	1 (1.5)	1 (2.5)	5 (11.6)
Toxic death	0	0	0
Grade ¾ toxicity			
Neutropenia	1 (1.5)	2 (5.1)	6 (13.9)
Anemia	1 (1.5)	1 (2.5)	2 (4.6)
Thrombocytopenia	0	0	2 (4.6)
Vomitting	3 (5)	4 (10.2)	4 (9.2)
Diarrhea	5 (8.4)	3 (7.6)	5 (11.6)

chemotherapy.

In a retrospective study with 85,000 patients with stage III disease using the National Cancer Database, the authors reported an increasing trend in favor of adjuvant chemotherapy by 22% in patients ≥80 years of age between 1990 and 1991, by 26% between 1995 and 1996, and by 39% between 2001 and 2002 [16]. Likewise, 68% of the patients ≥65 years of age received adjuvant chemotherapy in our study.

A meta-analysis evaluated the efficacy of FU/LV treatment in a total of 3351 patients with stage II/III who were operated on [4]. The patients were divided into four groups based on age including >50, 51-60, 61-70, and >70 years of age. The mortality rate was reduced by 24%, while recurrent disease was decreased by 32% in all patient groups. However, there were limited data on ECOG PS of elderly patients. In contrast, we assessed the efficacy of three chemotherapy regimens in patients ≥65 years of age based on the ECOG PS.

A Medicare database review revealed that 52% of the patients (N=4,768) with stage III colorectal cancer ≥65 years of age benefited from adjuvant chemotherapy. The mortality rate was reduced by 34% with FU treatment [3]. The lack of significant difference among the patient groups receiving or not adjuvant chemotherapy in our study can be attributed to the fact that most patients who did not receive adjuvant chemotherapy had early stage disease. In addition, the efficacy of FU treatment was also investigated by Sundararajan and colleagues [3]; however, the route of administration was not defined. In our study, however, OS and DFS were assessed based on the treatment given including FUFA infusion, weekly FUFA and oxaliplatin-based chemotherapy. Although FUFA infusion seemed to be more effective than other chemotherapeutic options in terms of DFS compared to FOLFOX-4 or weekly FUFA, it did not reach statistical significance. Additional oxaliplatin did not produce any statistical OS advantage in patients ≥65 years of age. This may be explained by the high number of patients with stage III disease in the group receiving FOLFOX-4 or decreased efficacy due to side effect-related dose modifications.

A SEER-Medicare database review demonstrated that survival increased with adjuvant chemotherapy in the elderly and kept increased, although it decreased with ageing [17]. Two other studies showed that one-third of elderly patients failed to complete six-month therapy [18,19]. Treatment failure was also associated with decreased survival rate. In our study, all patients completed treatment, except 15 patients in whom the dose was reduced or interrupted due to treatment-related side effects.

A meta-analysis of four randomized studies which included the data of 1567 patients on FOLFOX-4 regimen in metastatic disease or as adjuvant chemotherapy showed that 16% of the population was ≥70 years of age [20]. Patients ≥70 years of age had an increased risk of neutropenia and thrombocytopenia following FOLFOX. Similarly, the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) reported controversial data on the efficacy of oxaliplatin in geriatric population. Up-to-date data of this study suggested that oxaliplatin had an absolute effect on both OS and DFS in patients aged >65 years [21]. The efficacy of oxaliplatin in 35% of the substudy population ≥65 years of age showed no statistically significant difference in OS. In our study, we observed neutropenia and thrombocytopenia more often in patients receiving FOLFOX-4, however survival rates were similar to those receiving FU-based chemotherapy. Survival benefit might not be achieved in patients receiving FOLFOX-4, as these patients had advanced stage disease.

Furthermore, another study (NSABP-C07) which was the largest-scale analysis of patients and investigated oxaliplatin as a new generation agent in the adjuvant treatment of colorectal cancer showed similar OS rates in all age groups randomized to either 5-Fluorouracil/Leucovorin (5FULV) or 5FULV+oxaliplatin (FLOX) with a statistically higher DFS rates in patients receiving FLOX (p=0.002; HR 0.82; 95% CI 0.72-93) [22]. A subgroup analysis demonstrated an increased OS rate with FU plus oxaliplatin among patients <70 years of age [20]. However, there was no significant difference in the OS rate among these patients and those >70 years of age who received adjuvant oxaliplatin-based chemotherapy [20].

In the present study, although no statistical significance was noticed (which was possibly associated with the small sample size), we found increased DFS and OS in patients receiving infusional 5FU. Moreover, patients who were on oxaliplatin received FOLFOX infusion instead of FLOX regimen. Also, the geriatric patient population included individuals ≥65 years of age in our study, while the study mentioned above investigated patients aged ≥70 years. Furthermore, Goldberg and colleagues [20] reported similar grade 3/4 side effects in all age groups and unchanged side effect rates with additional oxaliplatin in the elderly. Despite the retrospective design of our study, the most common adverse effect was diarrhea in patients receiving adjuvant chemotherapy. The highest dose reduction due to toxicity was carried out in patients who were on oxaliplatin. In the MOSAIC study which was the largest study investigating the efficacy of adjuvant oxaliplatin in the treatment of colon cancer, the incidence of peripheral sensory neuropathy was 12%. No peripheral sensory neuropathy was observed in our study [21]. This can be attributed to the unsuccessful attempt to record such cases in the medical files.

In 55 patients the disease recurred, while 66 patients died during follow-up. This may be attributed to deaths from any cause due to increased comorbidities and short life expectancy in the elderly. Therefore, treatment should be tailored individually in elderly patients, considering possible comorbidities and life expectancy.

Other critical problems encountered in this age group are organ dysfunction and treatment discontinuation due to toxicity. Using SEER-Medicare database, Sharon et al. [18] reported that 78.2% of patients (N=2497/3193) ≥65 years of age completed adjuvant treatment with FU alone between 1991 and 1998. In contrast, our study included patients who received oxaliplatin-based regimens. Although one patient with FUFA infusion, 2 patients with weekly FUFA, and 5 patients with FOLFOX-4 experienced toxic side effects and 5 patients had delayed cycles, all completed adjuvant treatment.

Thomas et al. [23] reported that oxaliplatin-based regimens were nearly 80% of the adjuvant treatments for patients with stage II/III in 2007 and that elderly and patients with poor PS were less likely to receive oxaliplatin-based regimens. The authors also observed that 30% of elderly patients discontinued treatment within the first 3 months, indicating a 2-fold increase compared to FU-based regimens. In our study, however, dose reduction was more common in patients receiving FOLFOX-4 with a higher incidence of grade III/IV treatment-related side effects, although all patients completed their treatment.

All studies and analyses in geriatric populations were derived from retrospective data and subgroup analyses consisting of all age groups. However, these data may be insufficient to decide the best treatment in the elderly. Phase III studies including elderly patients still remain weak to generalize their outcomes due to lower incidence of comorbidities and better PS than overall geriatric population. Retrospective studies may recruit elderly patients with better PS for adjuvant treatment than those encountered in clinical practice. In our study, we found that ECOG PS was a major risk factor for OS on admission, irrespective of adjuvant treatment following surgery. Therefore, PS should be taken into consideration while deciding adjuvant treatment for elderly patients.

In conclusion, a thorough examination should be performed and possible side effects and prognostic features of the disease should be considered before tailoring individual adjuvant treatment following colorectal surgery for the elderly. Although no consensus on the optimal adjuvant treatment regimen has been reached upon yet, FUFA infusion seems to be an effective treatment choice. However, further prospective, randomized studies are required to identify specific patient groups that may be benefited from adjuvant treatments.

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