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ORIGINAL ARTICLE

Evaluation of the efficacy of adjuvant chemotherapy in patients with high-risk stage II colon cancer

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Summary

Purpose: *This study aimed at comparing the disease-free survival (DFS) in high-risk TNM stage II colon cancer patients who had been subjected to adjuvant chemotherapy and TNM low-risk stage II patients who did not receive chemotherapy.*

Methods: *: We retrospectively reviewed the medical records of stage II colon cancer patients between January 2006 and December 2011. High-risk patients were defined those with any colonic obstruction/perforation, mucinous histology, inadequate lymph node sampling, T4 disease, lymphatic/vascular or perineural invasion, preoperatively elevated carcinoembryonic antigen (CEA) and high-grade tumor. All patients with high-risk features received adjuvant chemotherapy.*

Results: *There were 42 patients in the high-risk treatment group and 21 patients in the non-treatment (observation) group. There were no significant differences in terms of gender, tumor size, tumor localization, or the number of excised lymph nodes between the groups. The median follow-up time was 33.9 months in the treatment group and 29.3 months in the non-treatment group. Recurrence developed in 4 patients (6.3%), 3 of which were in the treatment group. DFS in both groups was statistically similar.*

Conclusion: *Adjuvant chemotherapy in the high-risk patients resulted in similar DFS as that in the low-risk patients. Although the role of adjuvant chemotherapy for stage II colon cancer is unclear, it is rational to offer adjuvant chemotherapy to patients with high-risk stage II colon cancer.*

Key words: *breast cancer, ER, PR, HER 2, Ki -67, neoadjuvant chemotherapy*

Introduction

Colorectal cancer is a major cause of mortality in Western countries. It is estimated that there will be 103,170 new cases of colorectal cancer in the US and that 51,690 patients will die of this disease in 2012 [1]. Surgery is the curative treatment for colon cancer. The standard approach includes wide excision of the tumor and mesocolon, and associated lymphovascular tissues. Despite a potentially curative surgery, recurrences are common. Postoperative adjuvant chemotherapy is administered to eradicate micrometastases in such patients. Stage III patients are the primary group that benefits from adjuvant chemotherapy [2,3]. However, the efficacy of adjuvant chemotherapy in stage II patients is less clear in terms of DFS and overall survival (OS) [4-6]. Stage II patients have a relatively good prognosis and their 5-year survival rate is approximately 80% without adjuvant chemotherapy [7]. Nevertheless, 20% of these patients do recur during follow-up. Therefore, it is crucial to determine the subgroup of stage II colon cancer patients who would benefit from chemotherapy. Clinicopathological and molecular studies were performed to define the high-risk group of stage II patients [8-11]. Factors associated with poor prognosis include T4 disease [12], poorly differentiated histology and mucinous component [13], lymphovascular invasion [12],

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Table 1. Demographic data and tumor characteristics in the treatment and non-treatment groups

Characteristics	*Treatment group* *N = 42* *N (%)*	*Non-treatment group* *N = 21* *N (%)*	*p-value*
Mean age (years) ±SD	53.83 ± 13.0	64.9± 10.8	0.001
Median follow-up, months (range)	33.91 (8.7-57.1)	29.23 (4.3-60.2)	0.16
Gender			
Male	29 (69.0)	13 (61.9)	0.57
Female	13 (31.0)	8 (38.1)	
Tumor size			
T3	38 (90.5)	21(100)	0.29
T4	4 (9.5)	0 (0)	
Tumor differentiation			
Unknown	9 (21.4)	1 (4.8)	
Poor	6 (14.3)	2 (9.5)	NA
Intermediate	23 (54.8)	16 (76.2)	
Good	4 (9.5)	2 (9.5)	
Tumor localization			
Left + transverse	20 (47.6)	9 (42.8)	0.72
Distal (right)	22 (52.3)	12 (57.1)	
Lymph nodes excised			
<12	10 (26.1)	6 (28.8)	0.33
≥12	32 (73.8)	15 (71.4)	
Recurrence			
Absent	39 (92.9)	20 (7.1)	NA
Present	3 (7.1)	1 (4.8)	

NA:not assessable, SD: standard deviation

perineural invasion [12], bowel obstruction or perforation [14], close or positive margins [15], inadequately sampled lymph nodes [16], and elevated preoperative CEA level [12,17]. Although previous studies have demonstrated the influence of these factors on prognosis, data available to date have not clearly shown that adjuvant chemotherapy improves survival in high-risk patients [5,18].

The present study aimed at comparing DFS in high-risk stage II colon cancer patients who had been subjected to adjuvant chemotherapy and low-risk stage II patients who did not receive chemotherapy.

Methods

Patient selection

Clinicopathological data from the medical records of colon cancer patients treated at the Tulay Aktas Oncology Hospital between January 2006 and December 2011 were retrospectively reviewed. Clinicopathological features of the tumors (tumor size, grade, histopathological subtype, localization, and the number of lymph nodes excised) and patient socio-demographic data were recorded.

Risk definition

All patients were screened for high-risk factors at their initial presentation to our outpatient clinic. High-risk patients were defined as those with any of the following: colonic obstruction/perforation, mucinous adenocarcinoma, inadequate lymph node sampling, T4 disease, lymphatic/vascular or perineural invasion, elevated preoperative CEA and high-grade tumor. Patients that had none of these risk factors were regarded as low-risk. The choice of treatment was made according to prognostic factors as well as the clinician's preference.

Adjuvant chemotherapy

The high risk patients received bolus or infusional 5-FU-based regimens or oral 5-FU prodrug for adjuvant chemotherapy. The 5-FU bolus regimen included leucovorin 20 mg/m^2 bolus, days 1-5 and 5-FU 425 mg/m^2 bolus days 1-5 every 4 weeks for 6 cycles. The infusional 5-FU-based chemotherapy consisted of leucovorin 400 mg/m^2 i.v. over 2 h on day 1, followed by 400 mg/m^2 5-FU bolus and 1200mg/m^2/24-h infusion×2 days biweekly for 12 cycles. Oral 5-FU prodrug was capecitabine 2000mg/m^2 days 1-14 every 3 weeks for 24 weeks. The low-risk patients were followed up by routine physical examination, complete blood count, tumor markers, liver and renal function tests every

Table 2. High-risk factors in the treatment and non-treatment groups

High-risk factors	*Treatment group (N=42) N (%)*	*Non-treatment group (N=21) N (%)*	*p-value*
Colonic obstruction/perforation	6 (14.2)	0 (0)	NA
Mucinous adenocarcinoma	8 (19.0)	0 (0)	NA
Inadequate lymph node sampling	10 (23.8)	6 (28.5)	0.001
T4 disease	4 (9.5)	0 (0)	NA
Lymphatic/vascular or perineural invasion	4 (9.5)	0 (0)	NA
Preoperative CEA elevation	4 (9.5)	0 (0)	NA
High-grade tumor	6 (14.2)	0 (0)	NA

NA:not assessable

3 months. If there was suspicion for recurrence radiographic imaging was performed according to physician's choice. Assessments were performed every 3-6 months for 2 years, and then every 6 months for an additional 3 years.

Survival

DFS was recorded to determine any difference in recurrence between the treatment and non-treatment groups. DFS was the primary endpoint, which was defined as the time period from the date of diagnosis to the date of first documentation of disease recurrence.

Statistics

All statistical analyses were performed using SPSS for Windows. A two-sided p value <0.05 was considered statistically significant. Values were expressed as mean ± standard deviation. Categorical variables in both groups were compared using the x^2 test and the Fisher's exact test. DFS curves were constructed using the Kaplan-Meier analysis, and survival differences were determined by the log-rank test.

Results

Sixty-three stage II colon cancer patients were identified. The treatment group included 42 patients vs 21 patients in the non-treatment group. Median follow-up time in the treatment and non-treatment groups was 33.9 months (range 8.7-57.1) and 29.3 months (range 4.3-60.2), respectively. Patient and tumor characteristics are shown in Table 1.

There were no significant differences in terms of gender, tumor size, tumor localization, or the number of excised lymph nodes between the 2 groups; however, the mean age in the non-treatment group was higher. High-risk factors in the treatment group are shown in Table 2. In all, 6 patients in the non-treatment group had <12 lymph nodes excised, 4 of whom ≥80 years, had 9-11 lymph nodes excised, and had no other poor prognostic factors. They were not evaluated as high-risk by clinicians, whereas 2 patients with comorbid disease (coronary artery and cerebrovascular disease) did not receive chemotherapy despite the presence of high-risk factors. These 6 patients were disease-free during follow-up.

The treatment group received 5-FU-based chemotherapy (bolus 5-FU: N = 18, 42.8%; infusional 5-FU: N = 23, 54.7%; oral 5-FU prodrug: N = 1, 2.3%). Recurrence developed in 4 (6.3%) patients; 3 of them had received adjuvant chemotherapy, and subsequently developed liver and lung metastasis and 1 patient in the non-treatment group developed lymph node metastasis. DFS in both groups was similar (p>0.05) (Figure 1).

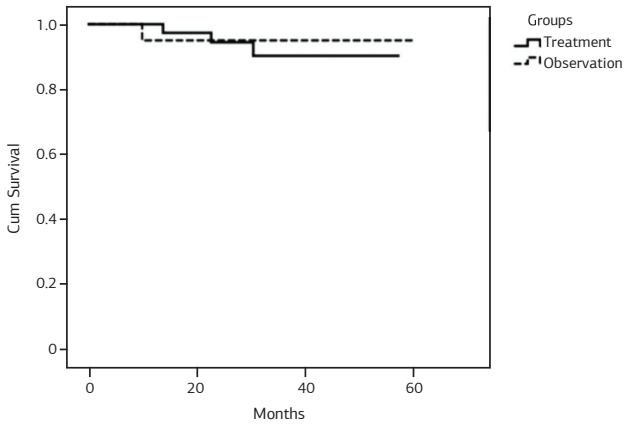

Figure 1. Disease-free survival between treatment and non-treatment groups (log rank, p=0.83).

Discussion

Adjuvant chemotherapy for colon cancer became a standard approach in the late 1980s with the introduction of 5-FU-based regimens [19,20]. Until 2004 different types of 5-FU infusions were used, though none was shown to be superior to the others, based on DFS and OS [21,22]. In 2004 the MOSAIC trial reported that the addition of oxaliplatin to 5-FU-based regimens improved DFS and OS in colon cancer patients [3]. Multiple trials of both oxaliplatin and 5-FU-based chemotherapy regimens in stage II and III colon cancer patients were conducted, and generally verified the statistically significant benefits in stage III groups, whereas subgroup analyses of stage II patients showed statistically non-significant improvement in OS and DFS in response to fluoropyrimidine-containing regimens [2,5,23].

The data regarding the benefit of adjuvant chemotherapy regimens in only stage II colon cancers are limited in number. The QUASAR trial reported better OS in stage II patients [5], whereas the IMPACT B2 trial reported non-significant 3% and 2% improvement in DFS and OS, respectively [23]. Meta-analyses and randomized trials also reported inconsistent findings [6,24-26], whereas a recent systematic review by Wu et al. reported a significant reduction in the risk of recurrence with chemotherapy [27].

In the present study chemotherapy was administered to patients regarded as high-risk, whereas patients that were considered as low-risk were only observed. The present findings show that there was no difference in DFS between the 2 groups. As such, we think that high-risk patients benefited from chemotherapy, as DFS was similar in both patient groups.

According to recent studies that used 3-year DFS as a surrogate for 5-year OS in adjuvant chemotherapy for colon cancer [28,29], the present study with nearly 3 years follow-up possesses a statistically valid time period for predicting survival.

Based on the SEER database, stage IIA colon cancer patients with T3N0 and stage IIB patients with T4N0 have 85% and 72% 5-year survival rates, respectively [30]. T4 disease alone is a high-risk factor associated with a 13% reduction in survival [30]. The effect of other risk factors on survival is less clear. To the best of our knowledge there are no available data that specify the percentage of survival reduction for other risk factors.

Some meta-analyses and population-based studies reported the effect of adjuvant chemotherapy in stage II colon cancer patients, but they lack prognostic features of patients. There is no consensus regarding the definition of high-risk stage II colon cancer patients. Apart from the pathologic features discussed above, ongoing studies on different molecular biomarkers are attempting to analyse the risk in patients and the response to chemotherapy [8-11]. Defective mismatch repair genes were reported to predict worse prognosis with fluoropyrimidines [31,32]. In the present study such gene analysis was not performed, as the patients were retrospectively evaluated. As the incidence of MMR gene mutation increases in right colon tumors and family history, considering the similar percentage of right colon tumors in both treatment and observation groups without any family history, we think that the results could not be interpreted due the lack of gene status.

In conclusion, the findings of the present study show that adjuvant chemotherapy in high-risk patients resulted in similar DFS compared to low-risk patients that did not receive treatment. We believe it is rational to discuss the chemotherapy option in high-risk stage II colon cancer patients. In the future, translational research will clearly define high-risk, based not only on pathology, but also on molecular markers, eventually making tailored chemotherapy alternatives for stage II colon cancer patients a real possibility.

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