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The Benefit and Tolerability of Adjuvant Chemotherapy in Elderly Stage III Colon Cancer Patients: A 3 Year Retrospective Audit

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Abstract

Objectives: The benefit of adding oxaliplatin to adjuvant fluoropyrimidine chemotherapy in patients >70 years is controversial. This retrospective audit investigated usage, benefit and tolerability of adjuvant chemotherapy for colon cancer in older adults.

Materials and methods: Patients aged >60 years with stage III colon cancer referred for adjuvant chemotherapy between 2010–2012 were identified from a tertiary hospital oncology database. Data were collected on demographics, chemotherapy received, completion rates, toxicities, relapse and survival. Comparison was made between the older group (age >70 years) and the younger group (age 60-70 years).

Results: 95 eligible patients were identified; 50 in the older group (median age 76), 45 in the younger group (median age 66), 56% male, 82% NZ European and 5% Maori. Older patients were less likely to receive adjuvant chemotherapy (76% and 91% in the older and younger group respectively, p=0.0017), especially oxaliplatin-containing regimens (14% and 47% of older and younger groups, respectively). Similar proportions in each group completed >80% of planned chemotherapy doses with no significant difference in early discontinuation due to toxicities. Survival was poorer in the older group (HR=2.90, 95% CI 1.40-5.47), including those who received chemotherapy (HR=3.22, 95% CI 1.42-6.88) but there was no significant difference in relapse-free survival between older and younger patients. Conclusion: Adjuvant chemotherapy was commonly offered to older adults with stage III colon cancer, although oxaliplatin was largely restricted to younger patients. While relapse-free survival was similar between age groups and chemotherapy types, older patients had poorer survival despite adjuvant chemotherapy.

Keywords: Colon cancer; Adjuvant chemotherapy; Elderly; Tolerability; Survival

Abbreviations

CRC: Colorectal Cancer; NZ: NewZealand; MOSAIC: Multicentre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer; 5-FU: 5-Fluorouracil; CCI: Charlson Comorbidity Index; ECOG PS: Eastern Co-operative Oncology Group Performance Status; TNM Staging: Tumour-Node-Metastasis Staging; RFS: Relapse-Free Survival; OS: Overall Survival; NCCN: National Comprehensive Cancer Network; PBCI: Pharmacy-Based Comorbidity Index

Introduction

Colorectal cancer (CRC) incidence in New Zealand (NZ) is amongst the highest in the world [1]. It is the third commonest malignancy in NZ after prostate and breast cancer, though its mortality is as high as that of the latter two cancers combined. Approximately one third of colon cancer patients present with stage III disease [2] involving regional lymph nodes but no distant metastases. With surgery alone, 5-year survival of stage III colon cancer is in the order of 45-60% [3,4]. The addition of 6 months of fluoropyrimidine chemotherapy following resection improves 5-year survival by an additional 7–11% [4,5]. Current guidelines on the choice of adjuvant chemotherapy for stage III colon cancer favour the addition of oxaliplatin to fluoropyrimidine chemotherapy for 6 months, which further reduces mortality by 3-4% [6-8].

Increasing age is a major risk factor for CRC, with peak incidence between 75-79 years of age [9]. Despite the higher prevalence of colon cancer in older adults, they are less likely to receive adjuvant therapies than younger patients [10]. In part this may be due to the elderly being more likely to have co-morbid illnesses and reduced physiologic reserve. They are more likely to be frail with reduced ability to restore homeostasis when the body is exposed to stressors, which leads to increased adverse outcomes [11]. Such considerations may also contribute to the elderly being poorly represented in clinical trials (only 14% of the cohort in the MOSAIC trial were aged over 70 years [6]), as could concerns about increased toxicity and reduced benefit of adjuvant chemotherapy in older patients. While these latter concerns were not borne out on a pooled analysis of three trials using adjuvant 5-fluorouracil (5-FU) with either Leucovorin or levamisole [5], toxicities were disproportionately higher in older patients when oxaliplatin was added to 5-FU-based adjuvant chemotherapy [12].

Whether the elderly benefit from adding oxaliplatin to adjuvant chemotherapy is also controversial. A favourable view comes from

analysis of large US observational data sets which reported that older patients appeared to derive as much benefit in survival from oxaliplatin as younger patients with stage III colon cancer treated with adjuvant chemotherapy [13]. In contrast, two large post hoc pooled analyses of randomised adjuvant chemotherapy trials of patients with stage III colon cancer found no significant survival benefit from adding oxaliplatin to fluoropyrimidine-based chemotherapy in patients aged over 70 years [14,15].

The purpose of this study was to evaluate the merit of adding oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy in older adults with colon cancer. We conducted a retrospective audit to compare the usage, benefit and tolerability of adjuvant chemotherapy in older versus younger patients with stage III colon cancer treated in our medical oncology service.

Materials and Methods

Study design, participants and setting

A retrospective review of paper and electronic patient records was conducted including all patients with stage III colon cancer aged 60 years and over who were referred for consideration of adjuvant chemotherapy to the Regional Cancer Centre at Waikato Hospital from January 2010 to December 2012 inclusive. Patients were identified from the Medical Oncology database, searching for stage III colon cancer and age 60 years and above. Patients were excluded if metastatic disease was diagnosed on staging investigations or if adjuvant treatment was delivered outside affiliated hospitals. Data on demographics, tumour characteristics, Charlson comorbidity index (CCI), Eastern co-operative oncology group (ECOG) performance status, date of surgery, details of any adjuvant chemotherapy (including reasons for not receiving chemotherapy), treatment completion rate, reasons for discontinuing chemotherapy, date of first relapse and date of death were collected. Data from patients in the older group (>70 years old) were compared with that from the younger group (60-70 years old).

Statistical analysis

Proportions, medians and means were used to describe patient and disease characteristics. Chi-square was used for analysis of proportions in patient, tumour and treatment characteristics. Log-rank statistic was used to analyse survival outcomes, with Kaplan-Meier curves plotted to calculate median overall survival and relapse-free survival (defined as first relapse event since surgery, censoring for death).

Ethics approval

Ethics approval was not required for this retrospective audit under Health and Disability Ethics Committees of NZ guidelines.

Results

Patient characteristics

Of 109 patients aged 60 years and over referred with stage III colon cancer during the three year period, 95 patients met the eligibility criteria. Seven patients were excluded due to metastatic disease, three due to treatment outside affiliated hospitals, two with stage II disease and two due to other reasons. Of the 95 patients included in the final analysis, 75 (79%) had a CCI of 0-1 and 87 (92%) had an ECOG performance status of 0-1, indicating a cohort of relatively fit elderly patients. Patient characteristics are detailed in Table 1; there were no statistically significant differences between the age groups with regards to gender, ethnicity, CCI, ECOG performance status and TNM tumour staging.

	60-70 years N = 45	**>70 years N=50**
Age, median (range) years	66 (60-70)	76 (71-85)
Gender, N (%)		
Male	25 (56)	28 (56)
Female	20 (44)	22 (44)
Ethnicity, N (%)		
Māori	3 (7)	2 (4)
NZ European	36 (80)	41 (82)
Asian	2 (4)	1 (2)
Other	4 (9)	6 (12)
ECOG performance status, N (%)		
0-1	42 (93)	45 (90)
>2	3 (7)	5 (10)
CCI score, N (%)		
0	29 (64)	28 (56)
1	8 (18)	10 (20)
2	2 (4)	9 (18)
3	4 (9)	1 (2)
4	1 (2)	2(4)
TNM tumour stage, N (%)		
T1	1 (2)	0
T2	3 (7)	8 (16)
T3	32 (71)	32 (64)
T4	9 (20)	10 (20)
TNM nodal stage, N (%)		
N1	36 (80)	33 (66)
N2	9 (20)	17 (34)
Histological grade, N (%)		
Not known	0	3 (6)
Well differentiated	0	3 (6)
Moderately differentiated	36 (80)	32 (64)
Poorly differentiated	9 (20)	12 (24)

Table 1: Eligible patient and disease characteristics.

Usage and tolerability of adjuvant chemotherapy

Younger patients were significantly more likely than older patients to receive any adjuvant chemotherapy (91% vs. 76%, p=0.0017) and oxaliplatin-based chemotherapy (47% vs. 14%; Table 2). Of those who did not receive adjuvant chemotherapy, the CCIs and ECOG performance status were similar between the two groups. Proportionately the older group had more patients who did not receive chemotherapy due to comorbidities while the younger group had more patients who did not receive chemotherapy due to postoperative complications. Of patients with a CCI score >2, only 1 of 12 patients over 70 years did not have chemotherapy, and 2 of 7 in the younger group.

Patient refusal of adjuvant chemotherapy was not significantly different between the two groups, accounting for 36% and 25% of those not treated with chemotherapy in the older group and the younger group respectively. Median time (range) from surgery to starting chemotherapy was 64 (26-123) days in the younger group and 67 (29-138) days in the older group.

Completion of >80% of planned chemotherapy doses was similar in both age cohorts, and for regimens with and without oxaliplatin (Table 2). While there were no statistically significant differences in the reasons for discontinuing chemotherapy early, proportionately more older patients stopped due to neurotoxicity when treated with oxaliplatin (3/7) than younger patients (7/21).

	60-70 years N = 45	**>70 years N=50**
Type of chemotherapy received, N (%)		
None	4 (9)	11 (22)
Oxaliplatin-based	21 (47)	7 (14)
5-FU/Leucovorin or capecitabine	20 (44)	32 (64)#
Completed > 80% of planned doses, N (%)		
Oxaliplatin-based	16 (76)	5 (71)
5-FU/Leucovorin or capecitabine	15 (75)	23 (72)
Reasons for no chemotherapy*, N (%)		
Patient choice Comorbidities	1 (25) 1 (25)	4 (36) 5 (45)
Postoperative complications	2 (50)	4 (36)
Reasons for discontinuing chemotherapy, N (%)		
Neurotoxicity	7 (17)	3 (8)
Other toxicity	9 (22)	12 (31)
Disease progression	1 (2)	4 (10)
Unknown/other	3 (7)	0
# P<0.002; * Could be more than one reason for each patient		

Table 2: Usage of adjuvant chemotherapy.

Benefit of adjuvant chemotherapy

Actuarial survival in those over 70 years old was significantly reduced compared with those aged 60-70 years (log rank p=0.004; Figure 1A) with 5 year survival of 49% and 82% respectively. While survival was poorer in those who did not receive chemotherapy, with only 50% of patients alive at 3 years in each group, no significant difference was found between the age groups (Figure 1B). In those who received adjuvant chemotherapy, with or without oxaliplatin, there was no significant difference in survival between the younger and older group either (Figure 1C and 1D).

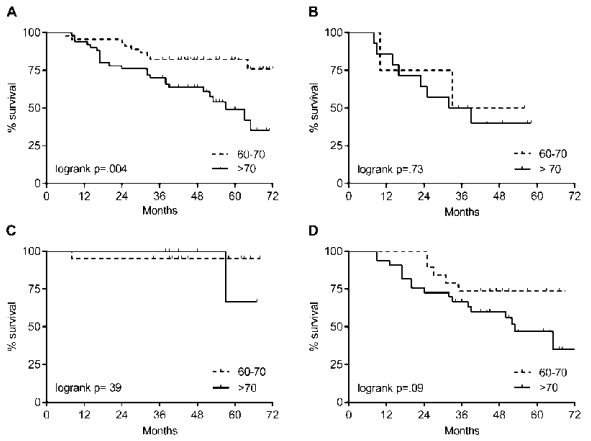

Figure 1: Survival outcomes grouped by age (60-70 years and >70 years). A: overall survival (OS) for the whole cohort; B: OS for patients not receiving chemotherapy; C: OS for patients receiving oxaliplatin; D: OS for patients receiving chemotherapy without oxaliplatin.

A higher CCI score (>2) did not predict for poorer survival with adjuvant chemotherapy in either age group (data not shown). Relapse-free survival (RFS) did not significantly differ by age group when compared within cohorts who did (Figure 2A) or did not (Figure 2B) receive chemotherapy, or who received adjuvant chemotherapy containing oxaliplatin or not (Figures 2C and 2D, respectively).

Discussion

This retrospective study sought to describe the pattern of usage, tolerability and outcomes with adjuvant chemotherapy in older patients with stage III colon cancer at our hospital, and investigated the controversial topic of whether oxaliplatin is tolerable and beneficial in those over 70 years of age.

Fewer patients over 70 years old received adjuvant chemotherapy after resected stage III colon cancer compared with those aged 60-70 years. However, our expectation that this discrepancy would be on the basis of medical comorbidities (as reflected in the CCI) or lack of fitness for chemotherapy was incorrect, as there was no significant difference in distribution of CCI or ECOG performance status scores between age groups. Similarly, while older patients were more likely to decline adjuvant chemotherapy (perhaps on the basis of preferring quality of remaining life over quantity), this trend was not statistically significant. More patients in the older group were excluded due to the

diagnosis of metastatic disease prior to commencement of adjuvant chemotherapy, suggesting that older patients may not have had adequate staging prior to their oncology assessment.

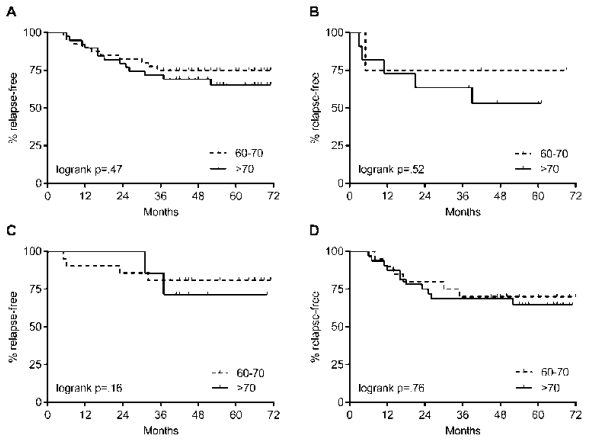

Figure 2: Relapse-free survival (RFS) outcomes grouped by age (60-70 years and >70 years). A: RFS for all patients receiving chemotherapy; B: RFS for patients not receiving chemotherapy; C: RFS for patients receiving oxaliplatin; D: RFS for patients receiving chemotherapy without oxaliplatin.

Within the cohorts who were treated with adjuvant chemotherapy, those over 70 years old were most commonly treated with either 5-FU/Leucovorin or capecitabine. Only a small minority (14%) received additional oxaliplatin, compared to 47% of those aged 60-70 years. This difference may be explained by the lack of consensus regarding the benefit of oxaliplatin in the elderly or concerns that co-morbidities made them unsuitable to receive such therapy, for example, pre-existing peripheral neuropathy, or greater vulnerability to this drug's toxicities [16]. The 14% rate of oxaliplatin use in the elderly group is much lower than that reported by Sanoff et al. in five US centres (37%-53%) [13]. The maximum eligibility age of 75 years in Sanoff's study resulted in a lower median age (69 years) compared to our study (75 years), which may have contributed to their higher rate of oxaliplatin usage, as would their likely adherence to NCCN guidelines, where offering oxaliplatin-based adjuvant chemotherapy is not restricted by age [17]. In our study, the ability of patients to tolerate adjuvant chemotherapy, whether containing oxaliplatin or not, was similar between the age groups. This suggests that the consultation between patients and their clinicians resulted in reasonably good selection of appropriate treatment for each patient, regardless of age, and only the fitter older people were treated with oxaliplatin-based chemotherapy.

The superior RFS seen in both age groups among patients who received oxaliplatin in their adjuvant chemotherapy compared to those who did not (6% in older patients and 10% in younger patients at five years) is consistent with the 6% improvement in disease-free survival reported at five years with oxaliplatin-containing regimens [6-8].

However, although the survival of the younger age group is comparable to that reported in randomised trials comparing 5-FU-based chemotherapy with or without oxaliplatin, the inferior survival of the older patients cannot be explained by the lower rates of oxaliplatin use in this cohort, as oxaliplatin only confers a 4% absolute improvement in overall survival [6-8]. Indeed, subgroup analysis of RFS by use of any chemotherapy or regimens with or without oxaliplatin showed remarkably similar RFS curves between the groups, with no statistically-significant differences (Figures 2A-2D). Even though some relapses may not have been recorded before death due to bowel cancer, the large survival difference between age cohorts treated with adjuvant chemotherapy in our study strongly suggests that the excess deaths in the older group were due to causes other than cancer.

Older age itself may account for the difference in survival between the older and younger groups. There is a seven year difference in remaining life expectancy in the general population aged 65 compared with those aged 75 [18]. Furthermore, a recent analysis of 25 clinical trials of adjuvant systemic therapy for colon cancer showed that increasing age had a disproportionately larger impact on short-term mortality than most variables, and much more than the treatment received [19].

While Ostenfeld et al. showed that increasing CCI was associated with poorer survival in patients with colorectal cancer [20], we found similar score distributions of CCI and ECOG PS between both patient age groups in our study. However, the CCI calculated in this study was not adjusted for age, and each additional decade of age over 50 increases the CCI by one point and the relative risk of death by 2.4 [21]. This could thus contribute to the inferior survival in the older age group in the absence of poorer RFS.

Charlson Comorbidity Index has been widely adopted as a measure of comorbidity in chemotherapy trials [21], while the ECOG scale is perhaps the most commonly used tool to assess performance status. Better tools are needed to assess an elderly patient's fitness for chemotherapy to optimize survival and avoid toxicity. There is more to assessing an older adult's fitness for treatment than merely counting the cumulative number of medical conditions as measured by the CCI, which does not take into account frailty, nutrition, functional and psychological status, social support, sensory impairment, falls and cognition. A systematic review of community dwelling persons over 65 years old has shown that the presence of any of seven geriatric syndromes (frailty, malnutrition, cognitive impairment and others) were independently associated with inferior survival compared to age matched controls [18].

A geriatric assessment tool for predicting chemotherapy toxicity in the elderly has been developed [16]. In addition, novel tools for measuring comorbidities predictive of mortality in cancer patients, such as C3 and pharmacy-based comorbidity index (PBCI) have also been investigated [22,23], where the C3 index was found to predict mortality more accurately in patients with colon cancer. Given the improved utility of these tools, their use in future studies and clinical practice may improve selection of treatment options for individual cancer patients.

Over half of the patients in both age groups who received adjuvant chemotherapy were not treated within 8 weeks of surgery, the current recommended guidelines [17]. A meta-analysis of studies evaluating the association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer showed that patients lost approximately 5% absolute survival benefit for each extra 4 weeks delay in starting chemotherapy after the first month after surgery [24,25]. Addressing resource constraints and patient management pathways to ensure that patients start adjuvant chemotherapy in a

timelier manner could improve survival to a similar degree as adding oxaliplatin.

Limitations of this study include the retrospective study design, the small sample size and lack of randomization, making it prone to confounders, selection bias and greater statistical error. The CCI score was calculated retrospectively from the medical record and the accuracy was dependent on the completeness of that record. In addition, it was not possible to collect information on or control for frailty, nutrition or functional status and other contributors to survival not captured by the CCI.

Only those patients referred to a medical oncologist were included in our study, and our population was not representative of all stage III colon cancer patients. If increased numbers of older patients were referred for assessment for adjuvant chemotherapy, we would likely see more frail patients but also additional older patients who may benefit from adjuvant treatment.

Despite the limitations, our study population presented data from 'real world' older community-dwelling colon cancer patients, rather than the 'trial eligible' population. The purpose of this study was to evaluate the merits of adding oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy. We found that the subset of older patients who were fit enough to be eligible for clinical trials benefited from oxaliplatin to a similar degree to younger patients. The challenge in clinical practice is to discriminate those from other older adults who are not fit enough to derive the benefit. A recent paper by Haller et al. [24] found a disease-free survival benefit from the addition of oxaliplatin to fluoropyrimidine regardless of age and medical comorbidities, although the effect was attenuated in those over 70 years of age, similar to our findings.

It is unlikely that further prospective randomised controlled trials will be conducted to evaluate the efficacy of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer in patients older than 70 years. While the results in this article in no way resolve the uncertainty of whether older adults benefit from the inclusion of oxaliplatin in adjuvant chemotherapy for stage III colon cancer, they do suggest that patients who are able to tolerate such treatment appear to benefit similarly, regardless of age. Further research could target the development of tools that would identify elderly patients who are fit enough to receive adjuvant chemotherapy (with or without oxaliplatin) and for whom the projected benefits are meaningful in the context of their remaining life expectancy.

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