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INTRODUCTION

COLORECTAL CANCER is predominantly a disease of the elderly, with over half of all deaths from this disease occurring in people over the age of 75 years [1]. Furthermore, the number of cases occurring in elderly people is expected to increase in the future as a result of population ageing. The primary treatment of colorectal cancer is surgical resection, but over half of all patients will eventually die of metastatic disease, which includes approximately 25% of patients who have evidence of metastases at the time of diagnosis [2].

Although the rate of progression of the disease is very variable, patients with advanced colorectal cancer have a median survival of only 6–9 months from the diagnosis of metastatic disease, during which time they may develop a wide variety of physical and psychological symptoms that detract from their quality of life and frequently precipitate hospital admission [3]. Since advanced colorectal cancer is usually incurable, the aims of treatment are prolongation of survival, effective symptom control and maintenance or improvement of quality of life (QoL). The adverse effects of chemotherapy must be weighed against any gain in survival, or improvement in cancer symptoms, a balance that will also be influenced by the choice of treatment and the expertise of the oncologist and supporting staff in selecting patients and managing side-effects [3]. In order to make such a judgement, these outcomes must be known for the patient group to which the treatment is to be offered.

Palliative chemotherapy is now offered to an increasing proportion of patients with advanced colorectal cancer due to recent advances which have resulted in increased response rates, a reduction in the side-effects of therapy and the demonstration of modest survival benefits, but there are good reasons to exercise caution in the use of this treatment in patients over 70 years of age.

WHY SHOULD ELDERLY PATIENTS BE CONSIDERED SEPARATELY?

Patients over 70 years of age form an extremely heterogeneous group as the cumulative effects of age-related physiological changes and comorbidities do not affect all individuals equally. Thus, the patient's physiological rather than chronological age should influence the choice of therapy. However, therapeutic decisions are often made on the basis of age alone, rather than more specific variables such as comorbidity, suitability for a particular type of intervention or the capacity to benefit [4, 5].

There is continuing uncertainty as to whether cancers behave more or less indolently in elderly individuals [6–9]. Age-related changes may alter the distribution and/or clearance of cytotoxic drugs in elderly patients [10–12], and the effectiveness of chemotherapy may be diminished and toxicity enhanced by pharmacodynamic changes [10, 11]. In some malignancies, the response to chemotherapy is lower and less durable among patients aged 60 years and over [13–15]. Molecular changes and changes in cell kinetics have been observed with a higher frequency in some tumours in elderly patients and may account for these differences [8, 10, 11, 16].

Predicting toxicity from chemotherapy is more difficult in elderly patients, in whom a combination of subtle defects in multiple organs may contribute to overall morbidity. Almost

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every organ system undergoes age-dependent change, which is associated with a decline in functional reserve that can reduce the ability to tolerate a stress such as that imposed by chemotherapy for advanced cancer. The frequency of comorbidity also increases with age, which additionally increases the risk of chemotherapy-related toxicity and/or impairs the ability of older people to tolerate such toxicity [17, 18]. Performance status has been widely used to select patients for entry into clinical trials, but it does not include a comprehensive evaluation of various age-related factors in elderly patients. A multidimensional geriatric assessment may be more sensitive in defining which elderly patients will tolerate chemotherapy [19, 20]. In addition to these physiological changes, older patients may also have different expectations of treatment compared with younger patients, which may influence the choice of treatment [21].

EVIDENCE FOR THE EFFECTIVENESS OF CHEMOTHERAPY FOR ADVANCED COLORECTAL CANCER

The best evidence of the effectiveness of healthcare interventions comes from the results of randomised controlled trials (RCTs). Although chemotherapy has been used in the treatment of advanced colorectal cancer for many years, there are relatively few published trials comparing chemotherapy + supportive care with supportive care alone in patients with advanced colorectal cancer. We have identified 12 trials comparing chemotherapy with no chemotherapy/supportive care in patients with advanced colorectal cancer [22–34]. Within all of these trials only approximately 1300 patients have been randomised. The trials are heterogeneous, examining different chemotherapy regimens and including different patient groups; unselected patients, asymptomatic patients, elderly patients, patients who have progressed after previous 5-fluorouracil (5-FU)-based chemotherapy and patients with disease confined to the liver who were given intrahepatic treatment. Many of the trials are confounded by the use of chemotherapy or other interventions in patients in the control group and hence these studies will tend to underestimate the survival benefits achievable with chemotherapy.

Despite these differences, the results are consistent; chemotherapy appears to improve survival by 3–6 months. QoL was assessed in only four of these trials, each using a different instrument [22, 26, 30, 34]. Three trials showed maintained or improved QoL for patients receiving chemotherapy [22, 26, 34], while one reported a greater reduction in QoL in patients who received chemotherapy that was ineffective [30]. A further trial showed prolongation of the symptom-free time in asymptomatic patients commencing chemotherapy at the time of diagnosis of metastatic disease compared with patients in whom chemotherapy was delayed until the onset of symptoms [32].

Thus, there appears to be some evidence that effective chemotherapy for advanced disease improves survival without any adverse impact on QoL. The issue that needs to be addressed is the generalisability of this evidence to patients over 70 years of age.

EVIDENCE FOR THE EFFECTIVENESS OF CHEMOTHERAPY IN ELDERLY PATIENTS

Although the majority of patients with advanced colorectal cancer are elderly, they have been under-represented in trials designed to assess the efficacy of palliative chemotherapy. Only one of the trials mentioned previously has examined the effectiveness of chemotherapy for advanced colorectal cancer in elderly patients [23, 24]. This trial, which has only been reported in abstract form, compared supportive care and weekly 5-FU (500 mg/m^2) + folinic acid (300 mg/m^2) for 6 months or until disease progression with supportive care alone in 163 patients with advanced carcinoma of the digestive tract, just over half of whom had colorectal cancer. The objective response rate was only 12.5%, but toxicity was said to be limited and reversible (16.4% grade 3 toxicity, no grade 4 or 5 toxicity) and there was a significant prolongation of survival in the group receiving chemotherapy. The majority of the remaining trials comparing chemotherapy + supportive care with supportive care alone specifically excluded patients over 75 years of age and the number of patients in the 70–75 year age group is likely to be small, highly selected and, therefore, may not be representative of the majority of patients in this age group.

The Gastrointestinal Tumour Study Group (GITSG) have undertaken a retrospective comparison of patients aged $\geq$70 years with patients aged $<$70 years who were included in a multi-institutional, randomised trial of 5-FU-based chemotherapy in metastatic colorectal cancer [35, 36]. 67 patients were 70 years or older (20.2% of all patients entered). The overall survival was worse for the older group in this study, but this difference was not statistically significant [35].

Limited information may be obtained from case series, as the criteria used for patient selection are not explicit so such studies may be subject to selection bias. In a comparison of 186 patients aged $\geq$70 years (median 73 years) with 658 patients $<$70 years (median 58 years) who received various 5-FU-containing regimens or raltitrexed for metastatic colorectal cancer, there were no significant differences in response rates or failure-free survival, but median overall survival was significantly shorter in the older patient group [37]. A study of chemotherapy in patients aged $\geq$70 years included 30 patients with advanced colorectal cancer aged 70–75 years, predominantly ECOG performance status 0 or I who received treatment with 5-FU and leucovorin [38]. The objective response rate, median duration of response and survival were similar to those seen in patients $<$70 years. Retrospective comparisons also suggest that the response rates to chemotherapy in elderly patients with advanced colorectal cancer are similar to those for younger patients [39, 40].

Overall, there is a paucity of evidence demonstrating the effectiveness of palliative chemotherapy for advanced colorectal cancer in elderly patients, meaning that clinical decisions regarding the use of this treatment in elderly patients are ill-informed and consequently more likely to be inappropriate.

TOXICITY OF CHEMOTHERAPY IN ELDERLY PATIENTS

Several 5-FU based chemotherapy regimens are widely employed as first-line therapy, but none has been established as a universally accepted standard therapy [41]. Although none of these regimens is clearly superior as far as survival is concerned, response rates and toxicity vary widely according to the schedule of 5-FU administration and the use of modulating agents such as leucovorin. The duration of palliative

chemotherapy treatment also varies widely [42, 43]. Despite the widespread use of combinations of 5-FU and leucovorin these regimens are associated with significant toxicity and require complex and inconvenient dosing schedules which often necessitate patients attending the hospital frequently [44].

Evidence regarding the specific toxicity of chemotherapy for advanced colorectal cancer in patients over 70 years is relatively sparse. Of the various toxicities of chemotherapy which appear to occur with greater frequency and severity in older people, mucositis, diarrhoea and myelosuppression are the most significant for patients receiving chemotherapy for advanced colorectal cancer as these are the dose-limiting toxicities of fluoropyrimidines. The development of concomitant severe leucopenia and mucositis is potentially life threatening. Mucosal damage secondary to chemotherapy may be more severe in elderly patients because ageing is associated with increased proliferation of the epithelial cells of the digestive mucosa, making these cells more susceptible to cycle-active substances and is also associated with a depletion of epithelial stem cells, which may delay the recovery from cytotoxic injury [45]. Ageing is associated with reduced functional bone marrow tissue, and an impaired ability to cope with haemopoietic stress. Exhaustion of the primitive haemopoietic stem cell reserve may compromise haemopoietic recovery from chemotherapy in older patients [46–48].

Only one small study has prospectively evaluated the toxicity of chemotherapy for advanced colorectal cancer in older compared with younger patients and the pattern and severity of side-effects were found to be similar [38]. However, mucositis and severe diarrhoea have been reported to occur more frequently in elderly patients receiving chemotherapy for advanced colorectal cancer and may represent a life-threatening complication [35, 49]. In the GITSG study, significant associations were found by univariate analysis between age and a number of toxicities, including any severe toxicity, leucopenia, diarrhoea, vomiting or death [49]. Multivariate analysis confirmed age to be a highly significant independent predictor of severe toxicity. Elderly patients in this study had a significantly greater tendency than younger patients to experience severe toxicity in multiple organ systems, an observation that has been made in other elderly patient groups receiving chemotherapy [50]. This may represent a direct effect of chemotherapy on multiple organ systems, or alternatively a cascade of secondary effects related to poor physiological reserves [49]. Fluoropyrimidine clearance is not measurably decreased in the elderly [51, 52], therefore, older patients may have increased sensitivity to damage at the cellular level from equivalent exposure to 5-FU [49]. The predisposition to toxicity in elderly patients seen in the GITSG study appeared to be not just a direct consequence of chemotherapy, but also of an age-related impairment in compensatory mechanisms which increased the risk of severe morbidity associated with diarrhoea [49].

Other studies have found less striking differences in toxicity in elderly patients. Simoni and colleagues retrospectively compared 92 patients >65 years (median age 68 years) recruited into three consecutive trials of 5-FU-based chemotherapy for advanced colorectal cancer with 148 patients aged <65 years [40]. Mucositis and myelotoxicity were more frequent in the elderly group, but overall, no significant difference in toxicity was evident between patients older than or younger than 65 years [40, 53]. Popescu and colleagues found no difference in grade III/IV toxicity in patients aged ≥70 years receiving various 5-FU-containing regimens or raltitrexed [37]. A further retrospective study has evaluated age as a risk factor for toxicity from irinotecan in patients with metastatic colorectal cancer who progressed within 6 months after 5-FU-based regimens [39]. 85 patients aged ≥65 years were compared with 90 patients aged <65 years. Average dose intensity was similar for both older and younger patients and no pharmacokinetic differences were detected. First course grade 3/4 diarrhoea, leucopenia, nausea and asthenia were more frequent in elderly patients, but differences were not statistically significant.

As these retrospective studies suggest that patients over 70 years of age may have an increased risk of significant treatment-related toxicity (myelosuppression, mucositis and/or diarrhoea) following palliative chemotherapy for advanced colorectal cancer, some clinicians may seek to minimise the toxicity of chemotherapy in elderly patients by dose reduction. However, there is good evidence that a dose response relationship exists for some solid tumours within the standard dosing range [54–57] and thus arbitrary dose reductions based on age could adversely affect outcome. New treatments may be associated with reduced toxicity, but limited information exists about the use of these agents in elderly patients [58, 59].

TREATMENT OUTCOMES

When assessing the value of chemotherapy for advanced colorectal cancer it is particularly important to consider the impact it may have on the QoL of those being treated [60]. This is particularly true for older patients with advanced colorectal cancer, whose life expectancy is short and who may have greater difficulty coping with their disease and disability, owing to the loss of social and economic resources generally available to younger people. Undoubtedly, palliative chemotherapy can be burdensome for patients as it is associated with a range of side-effects and may cause psychological distress, social isolation, financial difficulties and prolonged hospital stays [61]. Despite the evidence that chemotherapy for advanced colorectal cancer is effective, many patients with metastatic colorectal cancer are not being considered for palliative chemotherapy as some clinicians still feel that chemotherapy may adversely affect QoL [3, 62]. One reason for this may be that the majority of patients with advanced colorectal cancer are elderly.

At younger ages, postponement of death may be seen as the fundamental aim of treatment, but the primary aim of treatment in elderly patients is more likely to be an improvement in QoL [63]. Thus, for elderly patients it is not only important to consider their ability to withstand chemotherapy, but also their attitude towards chemotherapy and willingness to accept the risk of the potential trade-off between quality and quantity of life [61]. There is some evidence that elderly patients are less willing to trade survival for current QoL and may even be willing to accept a decrease in survival for an improvement in QoL [21, 64]. Elderly patients may, therefore, differ from younger patients in the priority they give to different treatment outcomes.

There is no information regarding the effect of palliative chemotherapy on QoL in elderly patients with advanced colorectal cancer. The trial discussed previously comparing palliative chemotherapy with supportive care in elderly patients did not assess quality of life. As the determinants of quality of life may change with age and as clinicians tend to under-

estimate older persons QoL compared with the patient's own judgement [65], further information regarding changes in patient assessed QoL is needed. This research should use a QoL instrument appropriate for elderly patients receiving chemotherapy for colorectal cancer in order to inform decision making in this patient group [66].

CONCLUSIONS

Although the results of randomised controlled trials suggest that palliative chemotherapy may prolong survival and maintain or improve quality of life in younger patients with advanced colorectal cancer, older patients have been underrepresented in these trials relative to the age-related incidence of this disease. The exclusion of older patients from clinical trials of chemotherapy for advanced colorectal cancer not only represents a missed research opportunity, but also has a direct impact on patient care, as there is inadequate evidence on which to base clinical decisions.

Elderly patients represent a heterogeneous group in terms of age-related physiological changes and comorbidities, which undoubtedly influence their likelihood of benefit from chemotherapy and ability to tolerate this treatment. Although the prevalence of comorbidity, functional limitations, and socioeconomic restrictions appear to increase with age, chronological age is a poor predictor of the extent of physiological changes in the individual. Elderly patients may benefit from anticancer therapy, but the therapeutic index of chemotherapy may be reduced in older people and there is no doubt that the ageing process increases the complexity of treatment. There is a need to better define the effects of palliative chemotherapy on survival, toxicity and QoL in elderly patients with advanced colorectal cancer. Further research is also required to enable the identification of those patients most likely to benefit from treatment and treatment regimens that are effective and tolerable when used in elderly patients.

At present there is insufficient evidence to support the routine use of chemotherapy for patients with advanced colorectal cancer over 70 years of age. However, such patients should be encouraged to enter well designed randomised trials in which patients are stratified by age and QoL is assessed using an appropriate age-calibrated instrument.

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In Western Europe, a quarter of the population is aged over 70 years, with a predicted increase to one-third of the population over the next two decades [1]. Improvements in healthcare combined with a falling birth rate have resulted in the older population increasing twice as rapidly as the total population. The majority of cancers occur in the elderly population, but until recently relatively little consideration has been given to treatment of cancer in the older patient.

Colorectal cancer is the second most frequent cause of cancer death with approximately 165 000 deaths per annum

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