CHEMOTHERAPY IN OLDER ADULTS WITH COLORECTAL CANCER

Claire Maddison,¹ Hu-Li Wong,² Peter Gibbs³
1. Department of Medical Oncology, Royal Melbourne Hospital, Parkville, Victoria.
2. Department of Medical Oncology, Eliza Hall Institute of Medical Research, Parkville, Victoria.
3. Department of Medical Oncology, Royal Melbourne Hospital, Parkville and Western Hospital Footscray, Victoria.
Email: claire.maddison@mh.org.au

Abstract
Colorectal cancer is the second most common cancer in Australia, with a median age at diagnosis of 70 years. With an aging population, the significance of this condition is increasing. Recent chemotherapy trials demonstrating improved outcomes have either excluded the elderly or demonstrated effectiveness in only a highly selected (well) population of older patients. Physiological changes that occur with increasing age and differences in the biology of the cancer itself create some uncertainty regarding the true benefit of chemotherapy for the majority of elderly patients, likely resulting in considerable undertreatment, either in the form of empirical dose reductions or abstention. For adjuvant treatment of stage III disease with 5-fluorouracil, pooled subgroup analyses of the small numbers of well elderly included in clinical trials and retrospective population studies suggest the elderly derive a similar benefit. However, the addition of oxaliplatin appears to provide no additional benefit at the expense of added toxicity. There are no studies indicating the optimal treatment in frail patients, though except where predicted lifespan is very short or there is a clear contraindication, adjuvant treatment should be considered. In the metastatic setting, there is similar evidence that fit elderly profit. Frail patients can be treated successfully and derive benefit from single agent 5-fluorouracil. Further studies involving elderly patients that are more representative of the majority are needed, and there is ongoing exploration of how more comprehensive geriatric assessment may help select the patients who are most likely to benefit from treatment, while minimising toxicity.

Background
Aging is associated with a number of physiological changes across most organ systems (table 1), some of which may influence the pharmacokinetics of chemotherapeutic agents. Many of these contribute to the reduced physiologic reserve of elderly patients and may affect both treatment tolerability and outcomes.

Australia’s population is aging. In 2011, 13.7% of Australians were aged ≥ 65 years and 1.6% were over 85; by 2056 estimates suggest 25% will be over 65 and 5-7% will be over 85.¹ The incidence of colorectal cancer, the second leading cause of cancer death in Australia,² increases with age, with a third of cases occurring in patients older than 75.³

As the elderly remain under-represented in clinical trials, including those for colorectal cancer,⁴,⁵ there remains uncertainty regarding the relevance of recent substantial treatment advances to older patients. There remains no universally accepted chronological age that defines an elderly person, making comparisons across studies that use differing definitions of ‘elderly’ challenging. Further, the small numbers of elderly patients included in clinical trials represent a highly selected population, with less comorbidity and polypharmacy, and better performance status and social supports than the majority seen in clinical practice.

Background
Aging is associated with a number of physiological changes across most organ systems (table 1), some of which may influence the pharmacokinetics of chemotherapeutic agents. Many of these contribute to the reduced physiologic reserve of elderly patients and may affect both treatment tolerability and outcomes.

Right-sided colon cancers,⁹ microsatellite instability (MSI),¹⁰ and BRAFV600E mutation,¹¹ have been reported at greater frequency with increasing age, and are thought to characterise tumorigenesis via the serrated neoplasia pathway.¹² While the clinical implications have yet to be clearly defined, right-sided and BRAF-mutant tumours have been separately associated with worse survival and distinct patterns of spread.¹³,¹⁴ Furthermore, screening colonoscopy may confer less protection from flat tumours located in the right colon.¹⁵ Conversely, MSI has an opposing positive prognostic effect, particularly in early stage colon cancer,¹⁰,¹⁶ and is associated with a lack of benefit from adjuvant 5-fluorouracil (5FU) chemotherapy.¹⁷

Older cancer patients are a heterogenous group, with the variable reductions in physiological reserve and rates of comorbidity not reliably captured in standard measures of function such as the Eastern Cooperative Oncology Group and Karnofsky performance status scales. Comprehensive geriatric assessment, including multi-disciplinary assessment of ability to complete activities of daily living, comorbidities, cognition, psycho-social status, nutritional stations, medication use and advanced care preferences can assist in predicting life expectancy and toxicity from chemotherapy, and in reducing morbidity.¹⁸,¹⁹ While obviously time and resource-consuming, more concise, standardised and validated tools are in development.

Despite subset analyses of the elderly patients enrolled in clinical trials concluding that fit elderly patients should
<table>
<thead>
<tr>
<th>System</th>
<th>Change</th>
<th>Examples of potential relevance</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>↑ sympathetic activity ) ↓ parasympathetic activity ) SBP ↑ arterial wall thickness ↓ ventricular compliance</td>
<td>↑ HT/vascular events with Bevacizumab ↑ coronary vasospasm with 5FU ↑ risk cardiac failure ↑ vasomotor instability may become exaggerated with volume depletion</td>
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<tr>
<td>Cerebrovascular/</td>
<td>↓ cerebral perfusion reserve ↓ response of cerebral blood flow to postural change Changes in cognition including memory Changes in myelin</td>
<td>↑ risk syncope/falls ↑ risk delirium ↑ risk peripheral neuropathy</td>
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<tr>
<td>Neurological</td>
<td></td>
<td></td>
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<tr>
<td>Renal</td>
<td>↓ renal blood flow ↓ renal mass ↓ GFR ↓ plasma renin-aldosterone levels ↓ concentrating ability</td>
<td>↑ risk volume depletion ↑ risk pre-renal renal impairment ↑ risk toxicity with renally cleared drugs (eg capecitabine) ↑ risk electrolyte disorders</td>
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<tr>
<td>Hepatic</td>
<td>↓ hepatic mass and blood flow ↓ cytochrome P450 content</td>
<td>Rarely of clinical significance on its own, but may be exaggerated by metastatic disease or comorbidities.</td>
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<tr>
<td>Gastrointestinal</td>
<td>Mucosal atrophy ↓ GI mucosal protective mechanisms ↓ gastric blood flow ↓ gastric and GI motility ↓ enzyme secretion</td>
<td>↓ absorption (rarely clinically significant) ↑ susceptibility to mucositis eg 5FU ↑ intestinal accumulation of a metabolite of irinotecan → may ↑ risk diarrhoea</td>
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<tr>
<td>Musculoskeletal</td>
<td>↑ sarcopenia ↑ bone loss ↓ balance (vestibular/CNS/musculoskeletal factors)</td>
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<td></td>
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<tr>
<td>Body composition</td>
<td>↓ muscle mass ↑ total body fat ↓ total body water ↓ albumin (but not in well elderly)</td>
<td>↑ volume distribution lipid soluble drugs → increased t1/2 ↓ volume distribution hydrophilic drugs → ↑ peak concentration</td>
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<td></td>
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<tr>
<td>Haemopoietic</td>
<td>↓ bone marrow reserve</td>
<td>↑ risk cytopenias (severity and duration)</td>
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<tr>
<td>Endocrine</td>
<td>↓ sex hormones Altered cortisol secretion Altered glucose metabolism</td>
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<tr>
<td>Immune</td>
<td>↓ T and B cell function Alterations in complement activation</td>
<td>↑ susceptibility to infection</td>
</tr>
</tbody>
</table>
receive standard chemotherapy doses, empirical age-related dose reductions are frequent in routine care. For example, in a recent survey of Australian oncologists, 23% reported routinely dose reducing in the fit elderly. While the potential for undertreatment is concerning, particularly in the adjuvant setting, many would argue that the experience of the select elderly entered on to research studies, does not reflect the reality of what can be safely delivered for the majority of older patients.

**Adjuvant treatment**

A5FU-based adjuvant treatment for stage III colon cancer reduces the risk of recurrence by 30% and cancer-related death by 25-30%. Capecitabine provides a similar benefit. A small additional survival benefit from the addition of oxaliplatin has also been demonstrated.

Subgroup analyses of outcomes for elderly patients in clinical trials, including pooled data from seven trials involving 3351 patients, suggest an equal benefit for elderly patients from use of adjuvant 5FU. Compared to surgery alone, receipt of 5FU/Leucovorin Calcium (LV) was associated with a hazard ratio (HR) for death of 0.76 (95% CI 0.68-0.85), corresponding to a 7% absolute improvement in five-year survival for all patients (71% v 64%), independent of age. Furthermore, increased age was not associated with a significantly increased risk of grade 3 or 4 nausea, vomiting, stomatitis or diarrhoea. There was a trend to increased rates of severe leucopenia.

An analysis of the X-ACT trial demonstrated that the equivalence of capecitabine was maintained in the 396 (20%) patients aged 70-75 years. However, fewer elderly (75-80 year-old) patients completed the planned course of treatment compared to younger patients (74% v 85%), with a trend for more dose modifications in older patients (61% v 51%).

In contrast to studies utilising a fluoropyrimidine alone, subgroup analyses from the two studies where oxaliplatin was added to 5FU, found no benefit from the addition of oxaliplatin in patients over 70 years of age. Further, the addition of oxaliplatin resulted in increased rates of neutropenia, thrombocytopenia and fatigue. Analysis of the MOSAIC trial found a significant increase in second cancers in older patients treated with oxaliplatin compared to younger patients (11% v 4%, p=0.001), with no age-related difference in the 5FU arm.

Retrospective analyses of cohorts from various clinical databases (table 2) have explored the benefit of 5FU/LV in ‘real world’ practice. Consistent with clinical trial data, these suggest a similar benefit for elderly patients, with infusional 5FU better tolerated than bolus.

Unfortunately, as the patients selected for treatment are

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Population/cohort</th>
<th>Overall survival (chemotherapy vs none)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham</td>
<td>27,805</td>
<td>32% 74-84 y/o</td>
<td>California Cancer Registry 1994-2006</td>
<td>HR 0.73, 95% CI 0.70-0.77</td>
</tr>
<tr>
<td>Jessup</td>
<td>26,600</td>
<td>30% 75-79 y/o</td>
<td>National Cancer Database 1990-2002</td>
<td>0.84, 95% CI not given</td>
</tr>
<tr>
<td>Steenbergen</td>
<td>8051</td>
<td>All ≥ 75</td>
<td>Netherlands Cancer Registry 1997-2009</td>
<td>HR 0.50, 95% CI 0.40-0.50</td>
</tr>
<tr>
<td>Sanoff</td>
<td>5498</td>
<td>All ≥ 75</td>
<td>2004-2007 SEER-Medicare, NYSER, NCCN, CanCCors</td>
<td>HR 0.60, 95% CI 0.53-0.68</td>
</tr>
<tr>
<td>Sundarajan</td>
<td>4768</td>
<td>All ≥ 65</td>
<td>SEER-Medicare 1992-1996</td>
<td>HR 0.66, 95% CI 0.60-0.73</td>
</tr>
</tbody>
</table>
inevitably a fitter population than those not treated, the impact of non-cancer deaths is a major confounder. Indeed, a number of studies report a greater survival benefit for adjuvant treatment than was observed in clinical trials enrolling young and fit patients, which seems implausible, particularly given the frequent use of routine chemotherapy dose reductions in older patients.20,27,28 In the absence of data on recurrence rates and cancer-specific mortality, the true impact of treatment remains uncertain.

Despite data demonstrating that the survival benefit of fluoropyrimidine-based treatment is maintained in older patients, use in practice inevitably declines with advancing age in multiple international series.27,29,30 Recent Australian data of 658 patients at Victorian hospitals treated from 2003 – 2012, reports higher overall treatment rates than data of 658 patients at Victorian hospitals treated from toxicity compared to younger patients.39 but their ability to do so may be limited by higher rates of age in multiple international series.27,29,30 Recent Australian patients, use in practice inevitably declines with advancing the entire course of chemoradiation do derive a benefit, select group of elderly patients who are able to complete have conflicting results. In general, it appears that the clear selection bias of population studies, many of which under-inclusion of the elderly in all clinical trials and the interpretation is much less than for adjuvant studies, where from competing causes of mortality confounding data disease being around 20 months, the likelihood of death in the AGITG MAX study, 47 the progression-free survival to 5FU/LV alone, demonstrated no significant interaction between age and treatment effect. No grade 3 or 4 toxicities were more frequent among the elderly patients.44 A subset analysis of pooled data from pivotal studies concluded that this agent maintained its efficacy and safety ratio in the selected elderly patients who enrolled.45

With ongoing uncertainty regarding the benefit of adjuvant chemotherapy for stage II colon cancer in younger patients,34 routine treatment of older patients with stage II cancers cannot be recommended. Elderly patients are less likely to receive chemoradiation for locally advanced rectal cancer.36-38 The evidence is similarly limited by under-inclusion of the elderly in all clinical trials and the clear selection bias of population studies, many of which have conflicting results. In general, it appears that the select group of elderly patients who are able to complete the entire course of chemoradiation do derive a benefit,38 but their ability to do so may be limited by higher rates of toxicity compared to younger patients.39

**Metastatic colorectal cancer**

The recent introduction of combination chemotherapy, with oxaliplatin and irinotecan, and biologic agents such as bevacizumab and cetuximab, has consistently seen survival in clinical studies approaching two years and beyond.

As with adjuvant treatment, there are a number of retrospective observational studies and analyses of the small numbers of elderly patients from clinical trials examining the efficacy and safety of all the various chemotherapeutic and biologic options for advanced disease. With life expectancy for patients with metastatic disease being around 20 months, the likelihood of death from competing causes of mortality confounding data interpretation is much less than for adjuvant studies, where survival at and beyond five years is more the focus. Folprecht et al retrospectively analysed data from 3825 patients who received 5FU-based treatment in 22 European trials between 1982 and 1996.40 For the 629 patients (16%) aged at least 70 years, response rates, progression-free survival and overall survival were similar to younger patients. A study of 339 patients who received second line irinotecan showed that patients over 70 years derived a similar benefit without increased toxicity.41 Ershler et al, reviewing capecitabine data from four studies, concluded that it was equally effective to 5FU/LV in elderly patients, with no evidence that the elderly experienced increased toxicity after adjustment for creatinine clearance.42 Other groups have similarly shown that the toxicity of capecitabine is not greater in the elderly if renal function is taken into account.43

A combined analysis of source data from four first-line phase 3 trials comparing irinotecan containing regimens to 5FU/LV alone, demonstrated no significant interaction between age and treatment effect. No grade 3 or 4 toxicities were more frequent among the elderly patients.44 A subset analysis of pooled data from pivotal studies concluded that this agent maintained its efficacy and safety ratio in the selected elderly patients who enrolled.45

The MRC FOCUS 246 study, a randomised trial specifically assessing outcomes in elderly and frail patients not fit for full dose chemotherapy due to age or frailty, showed that the addition of oxaliplatin at modified doses did not produce a progression-free or overall survival benefit. In a 2x2 factorial design, 459 older patients (median age 74 years, with 13% 80 years plus) were randomised to receive oxaliplatin with a fluoropyrimidine or fluoropyrimidine alone. With treatment initiated at 80% of standard dose, in the absence of significant toxicity, 35% of patients had planned dose escalations after six weeks, with 33% continuing at their initial dose. Further analyses suggested a negative effect on quality of life with oxaliplatin receipt. Other important findings of this study included similar efficacy and quality of life for 5FU versus capecitabine as single agents, but increased toxicity with capecitabine, including nausea, vomiting, anorexia and hand-foot syndrome.

In an analysis of the 99 (21%) patients aged 75-86 years in the AGITG MAX study,47 the progression-free survival benefit of adding bevacizumab to capecitabine was maintained. Other studies have also shown that the addition of bevacizumab to single agent 5FU irinotecan/5FU and oxaliplatin-containing regimens improves progression free survival to a similar extent in patients greater than 75 years old.48-51 An increased risk of thromboembolic events has been reported in many,52-54 but not all studies in these patients,47 mainly due to myocardial infarcts and strokes, with a hazard ratio of 2.5-3.0.55 Other toxicities, such as gastrointestinal perforation, proteinuria and bleeding, do not appear to be increased in the elderly. A recent prospective study of patients aged 65 or older,56 which importantly did include a geriatric assessment at baseline, reported an increase in severe toxicity in patients receiving bevacizumab in combination with chemotherapy. While this was predominantly due to an increased rate of hypertension, which in most instances is manageable with additional medication, the selection of patients who were to receive bevacizumab (lower in patients with heart disease) confounds comparison of treatment groups.
There is no apparent impact of age on the efficacy or the toxicity of cetuximab.\textsuperscript{57,59} As an example, a study of 614 patients included 49.7\% at least 66 years of age (range 18-89), with cetuximab given alone or in combination with irinotecan at the discretion of the treating physician.\textsuperscript{50} Response rate, progression-free survival and toxicity did not vary with age.

In an analysis of 2049 patients aged over 65 years using SEER-Medicare data from 2002 and 2005, 49\% of patients had received 5 fluorouracil folinic acid, 25\% irinotecan and 26\% oxaliplatin. Survival benefits associated with receipt of oxaliplatin or irinotecan were consistent across age groups, including those over 75 years.\textsuperscript{60} Another study of 2314 patients from the South Australian Clinical Registry found that, compared to patients less than 80 years old, those over 80 were less likely to receive chemotherapy (68.2\% v 29.2\%), less likely to receive combination therapy (74\% v 28\%) and had a significantly shorter median survival (19.2 months v 8.2 months).\textsuperscript{61} However, the median survival of those over 80 years who received any chemotherapy was similar to that of younger patients.

As with adjuvant therapy, chemotherapy receipt for metastatic disease in routine clinical care is inversely associated with age. In a retrospective cohort study of consecutive patients in the Netherlands between 2002 and 2007, only 19\% of patients over the age of 70 received palliative chemotherapy, whereas 64\% of those less than 70 received treatment.\textsuperscript{62} Where treated, the elderly are less likely to receive initial combination treatment, or to receive oxaliplatin, irinotecan and bevacizumab at any time.\textsuperscript{63} Similar findings were reported in a series of 864 consecutive metastatic CRC patients enrolled in the prospective Australian multicentre Treatment of Recurrent and Advanced Colorectal Cancer database since mid-2009, where 507 (59\%) patients were aged 65 years.\textsuperscript{63} In this cohort, 71\% received first-line chemotherapy, with 47\% also receiving bevacizumab. The use of first-line chemotherapy declined significantly with increasing age, from 83\% in patients aged 65-75 years to 36\% in those aged \( \geq \) 85 years. Older patients were also significantly less likely to receive combination regimens or bevacizumab.

**Conclusion**

With the elderly continuing to be underrepresented in clinical trials, and the elderly patients that are recruited being a select population, firm conclusions are difficult to reach. In the adjuvant setting, a number of pooled analyses of elderly patients from clinical trials and observational population studies suggest fluoropyrimidine-based treatment should be considered in fit older patients. With a healthy 75 year-old currently having a predicted life expectancy of more than 13 years for females and 11 years for males,\textsuperscript{64} the vast majority are likely to live long enough for recurrent cancer to impact their survival. With further advances in age, and diminishing life expectancy, the potential benefit of adjuvant therapy is reduced, and clinicians do need to become increasingly selective in the patients to whom they recommend treatment. The addition of oxaliplatin is not beneficial in patients over 70 years of age, and is also associated with an excess of early and late toxicity.

In the metastatic clinical cases, we similarly have evidence that the fit elderly benefit from palliative chemotherapy and targeted biological agents. In particular, cetuximab therapy appears to be equally well tolerated in the elderly, and with the exception of thromboembolic events, the same can be said for bevacizumab. The FOCUS 2 study suggests that single agent treatment with 5FU is a preferred strategy in frail patients. Further studies of this nature are critical to advancing our knowledge of the optimal treatment of older patients; the reality is that the majority of elderly patients are neither fit nor frail. It is for this group that more sophisticated methods of evaluation, such as comprehensive geriatric assessment, may help guide treatment decisions in the future and this remains a very active area of research.

**References**


