Review

Oral single-agent chemotherapy in older patients with solid tumours: A position paper from the International Society of Geriatric Oncology (SIOG)

L. Biganzoli a,⇑, S. Lichtman b, J.-P. Michel c, D. Papamichael d, E. Quoix e, C. Walko f, M. Aapro g

a Medical Oncology Department, New Prato Hospital, Istituto Toscano Tumori, via Suor Niccolina Infermiera, 20, 59100 Prato, Italy
b Memorial Sloan Kettering Cancer Center, New York, USA
c University of Geneva, Geneva, Switzerland
d Department of Medical Oncology, B.O. Cyprus Oncology Centre, Nicosia, Cyprus
e Department of Pneumology, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France
f H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
g Multidisciplinary Institute of Oncology, Clinique de Genolier, Genolier, Switzerland

Received 16 July 2015; accepted 9 August 2015

KEYWORDS
Oral chemotherapy
Older patients
Breast cancer
Lung cancer
Colorectal cancer
Metronomic therapy
Vinorelbine
Capecitabine
Bevacizumab

Abstract  Compared with intravenous (i.v.) chemotherapy, oral administration is convenient, requires fewer healthcare resources, is generally preferred by patients, and may be appropriate in older people with breast, colorectal and lung cancers. The effects of organ dysfunction on drug metabolism and drug interactions in patients with multiple comorbidities must be considered but are not specific to oral chemotherapy. Single-agent oral chemotherapy with capecitabine or vinorelbine is active in older patients with advanced or metastatic breast cancer. Choice of treatment is based mainly on different safety profiles. In the adjuvant treatment of colorectal cancer (CRC), single-agent oral capecitabine is an effective alternative to i.v. fluorouracil (5-FU) regimens. In metastatic CRC, oral, single-agent capecitabine has recently shown encouraging median overall survival in combination with bevacizumab. In non-small cell lung cancer, fit older patients, like their younger counterparts, benefit from...
1. Introduction

Older cancer patients are under-represented in clinical trials [1–3], resulting in a lack of evidence on how they should be treated. Account may be taken of drug elimination pathways and the effects of ageing on renal function, and empiric dose adjustments made [4]. But use of modified chemotherapy schedules that have not been adequately assessed is frequent, and under-treatment is common [5].

While ageing varies greatly in speed, the common trajectory is from robust health to frailty and in many cases disability [6]. Comorbidities accumulate so that cancer co-exists with equally significant and interlinked conditions such as heart failure and chronic kidney disease [7]. Even so, a male aged 80 unaffected by cancer can expect a further 8 years of life, and women a further 10 [8]. In cancer-affected patients, our task is to extend life towards that norm and improve or maintain its quality. For older cancer patients particularly, balancing treatment efficacy and quality of life is an especially delicate task. Use of oral anti-cancer agents may play a part.

Oral cytotoxics are increasingly challenging the dominance of intravenous (i.v.) drugs, and there are now at least 20 such agents [9]. Interest in oral agents is driven in part by convenience and ease of administration, the avoidance of morbidity associated with long-term central venous access and reduced utilisation of healthcare facilities [10]. But patient preference is also a factor [11]. Oral drugs suit those leading an active life, and are generally favoured by patients. Oral agents are also being used in older patients. However, among these patients adherence may be a particularly important issue, especially in the presence of cognitive impairment. Under-treatment, resulting in reduced efficacy, and over-treatment, causing unnecessary toxicity, are both potential problems (Table 1).

Given this background, a committee met in 2014 under the auspices of the International Society for Geriatric Oncology (Société International d’Oncologie Gériatrique, SIOG) to assess options for the treatment of older patients who may be suited to single-agent oral chemotherapy. The literature was searched by individual participants and further searches have been made since the initial meeting. Because randomised clinical trials in the area are few, the opinions of this SIOG Task Force are those of informed experts. No formal levels of evidence are ascribed.

This paper considers issues of patient preference and adherence and the current position of oral therapy by tumour type and drug. Where relevant data are available, we concentrate on those relating to older patients.

2. Patient preference and adherence

Women with breast cancer undergoing oral, non-hormonal treatment report that their lives are less affected by therapy than those on i.v. drugs and feel greater autonomy in handling their disease [11]. Given equal efficacy, 89% of women on oral therapy said they would choose oral over i.v. treatment and 67% of those on i.v. drugs also said they would prefer an oral regimen. The majority believed that oral chemotherapy was as effective as i.v. This finding may help resolve the concern that breast cancer patients perceive oral treatments as less effective [12].

The women surveyed by Schott et al. were generally not worried that they might take their medicines incorrectly [11]. However, adherence with oral treatment continues to be a concern in all branches of medicine [13–19]. This is especially so when patients are asked to take many tablets, when dosing regimens are complex or intermittent, and when patients are older and potentially cognitively impaired [13–15,19–21].

2.1. Adherence studies in general

A recent review of nine US studies of patients aged 65 and older reported that non-adherence was associated with poorer health knowledge and cognitive function, less discussion between physician and patient about their condition, presence of drug side effects and polypharmacy [19]. The relationship between poor adherence and a large number of different drugs to be taken seemed the most consistently reported negative factor. The studies reviewed (which used heterogeneous methodologies) related to type II diabetes, overactive bladder, hypertension, hyperlipidaemia, coronary heart disease and memory disorders. None related to cancer. It would be reasonable to expect that the barriers to adherence would extrapolate to oncology. However, there may be factors specific to the way cancer is perceived and the particular circumstances of the cancer patient. And it is worth noting that the results of studies into adherence are sometimes counterintuitive. For example, Feil et al. found that the presence of a
caregiver did not reduce the risk that a diabetes patient would adhere poorly to therapy and experience inadequate glycaemic control [20].

However, Feil et al. did find the expected negative effect of cognitive impairment on adherence, and the role of cognitive function is reflected in the wider literature. A systematic review of studies that looked specifically at older adults with cognitive impairment found that inability to understand new directions, living alone and difficulty scheduling medications into the daily routine were among the barriers to adherence [21]. So too was the use of inappropriate medications. The review found only three studies of cognitively impaired patients that had sought to improve adherence through intervention. The only one to show benefit used telephone or televideo reminders at each dosing interval.

2.2. Adherence studies in cancer patients

Among adult patients on oral anticancer agents, adherence rates ranging from 55% to 95% are reported [9]. The majority of adherence studies have been of endocrine agents in early breast cancer (EBC), where evidence suggests early discontinuation and non-adherence compromise efficacy. Thus Hershman et al. found that around a third of women (of any age) who began adjuvant hormonal therapy in the period 1996-2007 subsequently discontinued treatment [22]. Of those who continued, 28% were non-adherent. Both non-continuation and non-adherence were significant independent predictors of mortality.

Even in the adjuvant context, there is little specific knowledge about older patients. However, the Breast International Group (BIG) 1–98 trial offers some insights [23]. In this study comparing letrozole against tamoxifen in endocrine responsive early breast cancer, the 6% of patients aged 65 and over were less likely than younger patients to complete 5 years of therapy (23% versus 38% respectively). However, discontinuation was due primarily to AEs and disease progression, rather than lack of adherence per se. And the disease-free survival (DFS) benefit of letrozole over tamoxifen was similar in all age groups.

Discussion is usually framed in terms of the reduced therapeutic efficacy expected to follow suboptimal drug exposure. In the context of highly toxic drugs, over-adherence – which may be caused by a patient’s belief that “more is better” – and the continuation of therapy in the face of clear toxicities which should prompt discontinuation or dose reduction – are also potential problems [16]. Diarrhoea is particularly relevant to older patients with reduced mobility. Quite apart from the distress, this toxicity – along with vomiting – may be responsible for reduced absorption of oral drugs.

In all patients, promoting adherence requires appropriate explanation about the nature and benefits of treatment, as well as about how to respond to toxicities. Along with oncologists, geriatricians, nurse practitioners and pharmacists should be involved in this task. The specialities of geriatric pharmacy and geriatric pharmacology have a growing role given the prevalence of polypharmacy and the need to take into account interactions with both prescribed drugs and complementary medicines [24,25].

The literature contains important insights into factors related to adherence with oral therapy in patients, including the old, with a range of diseases. However, the extent to which these factors can be modified is less clear. Certain studies have looked specifically at compliance with oral cancer treatment. Few studies have considered adherence with oral therapy among cancer patients who are old. However, in a recent trial of adjuvant oral capecitabine in 161 breast cancer patients aged 65 and older, 78% took at least 80% of prescribed doses [15].

3. Oral chemotherapy in older patients

3.1. Metastatic breast cancer

In metastatic breast cancer (MBC) unresponsive to endocrine agents, there is no gold standard therapy. According to the 2012 European Society for Medical Oncology (ESMO) guidelines, single agents should be considered as an option alongside combination regimens [26]. The most recent SIOG/EUSOMA guidelines on elderly breast cancer also regard oral therapy as an option [27]. Treatment should be tailored to patient preference, comorbidities, tumour biology, disease-free interval, tumour burden, the presence or otherwise of aggressive visceral metastases and prior therapies [28].

Non-anthracycline, non-taxane regimens are appropriate for patients who have been exposed to these agents in the adjuvant or neoadjuvant settings. Single-agent oral chemotherapy with vinorelbine or capecitabine may be helpful in elderly patients and, more widely, among patients without directly life-threatening or severely symptomatic disease. Among such patients, there are no survival data to support the superiority of one agent or combination over another. However, agents differ in their toxicities: for example, in the randomised European Organisation for Research and Treatment of Cancer (EORTC) trial of single agent vinorelbine and capecitabine in anthracycline and taxane pre-treated MBC, the incidence of haematological and neurotoxicity and nausea/vomiting was higher with vinorelbine than with capecitabine while the reverse was true for diarrhoea and hand-foot syndrome (HFS) [29].

3.1.1. Capecitabine

In MBC, the oral fluoropyrimidine capecitabine is a standard of care in patients pre-treated with anthracyclines and taxanes; and it has potential first-line in slowly
progressive disease. However, adequate renal function is particularly important with oral administration [30]. While pharmacokinetic (PK) data suggest no difference in the level of active metabolites in patients aged over 60, those with severe renal impairment should not be given the drug, and patients with mild to moderate renal dysfunction should be closely monitored [31]. Regardless of age, interaction with warfarin should be considered since capecitabine significantly increases its anticoagulant activity [32,33].

The registered capecitabine dose is 1250 mg/m² twice daily for 2 weeks, with 1 week off. However, a starting dose of 1000 mg/m² may reduce toxicity, enable longer treatment and extend disease control [34,35]. Details of single agent capecitabine studies are given in Table 2.

It has been suggested that capecitabine toxicities and the need for dose adjustment may be reduced without influencing anti-tumour efficacy by concomitant 50 mg po pyridoxine [41]. However, a recent meta-analysis concluded that the only intervention with good evidence of efficacy in reducing HFS is celecoxib [42].

Recently, the OMEGA trial set out to compare pegylated liposomal doxorubicin against capecitabine first-line in patients aged at least 65 years [43]. However, the study was closed to accrual with only 78 patients randomised.

### 3.1.2. Vinorelbine

Oral vinorelbine (not available in the US) 60 and 80 mg/m² produces AUCs equivalent to i.v. doses of 25 and 30 mg/m² respectively [44]. Although there has been no direct comparison, single-agent oral and i.v. vinorelbine seem similarly effective. In a phase II study (Table 2) the median 24 month overall survival (OS) was comparable with the median 18 months expected with single-agent i.v. vinorelbine [45]. The principle toxicity was haematological, but – although 42% of patients had grade 3–4 neutropenia – the 4% incidence of febrile neutropenia was comfortably below the threshold for automatic prophylactic granulocyte-colony stimulating factor (G-CSF). Although regarded as only moderately emetogenic, oral vinorelbine causes appreciable nausea, and this may reduce adherence to treatment if administration is not accompanied by prophylactic anti-emetics. Data on oral vinorelbine in breast cancer patients, including the elderly, are presented in Table 2.

### 3.2. Colorectal cancer

The treatment of elderly patients with colorectal cancer (CRC) has recently been considered by a SIOG Task Force [48].

#### 3.2.1. Adjuvant therapy

Pooled analysis of seven randomised trials concluded that older stage II/III CRC patients fit for inclusion in studies derived the same benefit from 5-FU based adjuvant chemotherapy as their younger counterparts [49]. O’Connor et al.’s retrospective analysis of more than 18,000 patients aged 66 years and older found no benefit from adjuvant therapy [50]. Based on a study of 3000 stage II patients randomised to 5-FU/FA or observation, the Quasar Group concluded that adjuvant chemotherapy was likely to have a small beneficial effect on survival, although not in patients aged 70 or over [51]. Therefore adjuvant therapy in elderly stage II patients should not be considered as standard.

In the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial, patients with resected stage III colon cancer randomised to capecitabine experienced less toxicity overall than those assigned to the Mayo regimen of 5-FU plus folinic acid (FA), though the latter was more toxic [52]. The toxicity profile of capecitabine in patients aged over 65 years was similar to that in younger patients. With a median follow-up of 6.9 years, capecitabine is at least equivalent to 5-FU/FA in maintaining DFS and OS. This is also true in the subgroup aged 70 and over [53]. In relation to the newer regimens, the most recent evidence from the Adjuvant Colon Cancer Endpoints (ACCENT) database suggests that, while oxaliplatin in combination with infusional fluorouracil and leucovorin (FOLFOX) is a standard adjuvant option in general, patients aged 70 years and older derive little or no benefit from the addition of oxaliplatin to fluoropyrimidines [54]. Among more than 5000 patients under 70 drawn from three trials, use of an oxaliplatin combination was associated with an improved hazard ratio (HR) for OS of 0.83 (0.74–0.92) compared with i.v. FU. However, among more than a thousand patients aged 70 and over, the HR was 1.04 (0.85–1.27). The corresponding HRs for DFS were 0.78 (0.71–0.86) and 0.94 (0.78–1.13). Moreover, deaths within 6 months of therapy were higher (though non-significantly so) among oxaliplatin-treated elderly patients than among controls (3.2% versus 2.3%).

ACCENT does not include information on comorbidities, toxicities or dose intensity – any of which may...
influence the interaction between age and the oxaliplatin combination regimens. Another potential difficulty is that different fluoropyrimidine regimens (oral as well as i.v.) were included. The addition of oxaliplatin to adjuvant therapy in stage III patients aged 70 and over can be discussed, based on individual circumstances. Any benefit is incremental, and side-effects such as peripheral neuropathy can be troublesome and long-lasting. Fluoropyrimidine monotherapy remains an effective option. Within this approach, oral capecitabine is an appropriate choice.

### 3.2.2. Metastatic disease

Over the past 30 years, survival among synchronous metastatic CRC patients included in registries has doubled to around 10 months [55]. However, such unselected patients survive only half as long as those in recent clinical trials; and the survival improvement in registry populations is disproportionately accounted for by younger patients. This is also true within trials, which include few older patients [54].

The possibility of conducting trials specifically in old and frail patients is shown by the recent MRC FOCUS2 study [38]. Patients with previously untreated advanced CRC unfit for full dose chemotherapy were randomised to 1st-line; 60 mg/m\(^2\) increased to 80 mg if no neutropenia, at least 4 cycles

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum et al. [36]</td>
<td>Retrospective analysis of 805 pts in ph II/III studies</td>
<td>Ist line: RR 25%; median OS 22 months</td>
</tr>
<tr>
<td>Stockler et al. [37]</td>
<td>Comparison vs CMF in pts unsuited to intensive chemo</td>
<td>1st line: RR 19%; OS 13 mo</td>
</tr>
<tr>
<td>Bedard et al.</td>
<td>Three studies were at 1250 mg/m(^2) bd for two weeks; one at 1000 mg/m(^2) bd, first line</td>
<td>Capcitabine achieved longer OS (22 versus 18 months, (p = 0.02)) and was better tolerated</td>
</tr>
<tr>
<td>Bajetta et al. [39]</td>
<td>Dose reduced to 1000 mg/m(^2) after early toxicity at 1250 mg/m(^2) bd for two weeks; one at 1000 mg/m(^2) bd, first line</td>
<td>Two toxic deaths in first 30 pts; RR 35% and less toxicity in subsequent 43 pts</td>
</tr>
<tr>
<td>De Sanetis et al. [40]</td>
<td>N = 75; median age 76 yrs; disease control after 3 cycles in 81%; stable disease maintained for at least 12 cycles in 17%; Gr 3 diarrhoea in 12% and HFS and stomatitis in 8%</td>
<td></td>
</tr>
</tbody>
</table>

Davidoff et al. identified more than 20,000 non small cell lung cancer (NSCLC) patients aged over 65 in the Surveillance, Epidemiology, and End Results (SEER) database and found that only 26% had first-line chemotherapy [58]. Treatment with platinum doublets decreased with age, comorbidity and poor performance status (PS). Yet such doublets improved survival even when adjustment was made for these factors; and their
Table 3
Studies of metronomic therapy.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Population</th>
<th>Study (ref)</th>
<th>Regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced breast cancer</td>
<td>No minimum age</td>
<td>Dellapasqua et al. [67]</td>
<td>Cyclophosphamide 50 mg/d C + 45 mg/m² d1–8 q 2 w</td>
<td>RR 48%</td>
</tr>
<tr>
<td></td>
<td>T2 + ER + ve pts aged &gt;70 yrs unsuited to conventional chemotherapy</td>
<td>Bottini et al. [68]</td>
<td>Capcitabine 500 mg tid B + 45 mg/m² d1–8 q 2 w</td>
<td>Median TTP 42 weeks Minimal toxicity</td>
</tr>
<tr>
<td></td>
<td>Women with at least one prior endocrine therapy for M+ disease; mean age 65 yrs</td>
<td>Schwartzberg et al. [69]</td>
<td>Letrozole with or without cyclophosphamide 50 mg/d L + 45 mg/m² d1–8 q 2 w</td>
<td>RR higher (88% versus 72%) in pts receiving additional cyclophosphamide; and VEGF expression significantly less than with letrozole monotherapy</td>
</tr>
<tr>
<td></td>
<td>ER + ve, postmenopausal women; no lower age limit</td>
<td>Aurilio et al. [70]</td>
<td>Cyclophosphamide 1500 or 2000 mg given in divided doses, added to intravenous (i.v.) fulvestrant Cyclophosphamide 2.5 mg/d and methotrexate 2.5 mg bd on d 1 and 4 added to im fulvestrant</td>
<td>Activity described as substantial and toxicity as low; HFS most frequent AE, but Gr3 or greater in fewer than 10%</td>
</tr>
<tr>
<td>Advanced cancer phase I</td>
<td>No lower limit on age</td>
<td>Rajdev et al. [71]</td>
<td>Metronomic oral vinorelbine Methotrexate 2.5 mg bd on d 1 and 4 added to im fulvestrant</td>
<td>Long term disease control achieved with minimal toxicity</td>
</tr>
<tr>
<td>NSCLC stage IIIb/IV</td>
<td>First line; aged over 70 years (median 79 years); median 3.5 serious comorbidities</td>
<td>Camerini et al. [63]</td>
<td>Oral vinorelbine 50 mg three times per week until progression</td>
<td>ORR only 13% but 50% had SD for &gt;12 weeks; median OS 9.5 months. Only 4 episodes of Gr 3 (and no Gr 4) toxicity in 32 pts</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Recurrent, platinum resistant</td>
<td>Barber et al. [72]</td>
<td>Cyclophosphamide 50 mg/d plus bevacizumab</td>
<td>RR 42% OS 20 months in responders, but only 9mo in non-responders</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>Garcia[73]</td>
<td></td>
<td>Median OS 17 months</td>
</tr>
</tbody>
</table>

use was associated with greater one-year survival compared with single agents. The phase III trial by Quoix et al. in patients aged 70–89 years, justifies a similar conclusion [59]. Despite greater toxicity (neutropenia 48% versus 12%), carboplatin plus paclitaxel significantly improved OS (median 10.3 versus 6.2 months) compared with vinorelbine or gemcitabine monotherapy.

The 2012 ESMO NSCLC guidelines suggest a range of first-line options for advanced disease, with the choice dependent on histology, molecular pathology, age, PS, comorbidities and patient preference [60]. A phase II study of 98 previously untreated stage IIIb-V patients (median age 63) randomised to oral or i.v. vinorelbine showed that the two forms of administration were comparable in activity [61]. Median OS with oral vinorelbine was 9.3 months and 7.9 months with i.v. drug. Forty-one percent of patients treated with oral vinorelbine were alive at 1 year, and 29% of those in the i.v. group. Grade 3–4 neutropenia was experienced by 46% and 62% respectively. Patients received either i.v. vinorelbine 30 mg/m² per week or oral drug at 60 mg/m² per week for 3 weeks increased to 80 mg/m²/week in the absence of severe neutropenia. Eighty-five percent of patients were able to escalate the oral dose, and relative dose intensity was higher with oral than with i.v. (89% versus 76%). Non-haematological toxicities were mild to moderate and similar across groups.

Relating specifically to older patients, 43 patients aged 70 or older with ECOG PS 2 or more treated with vinorelbine 60 mg/m² d1–8 q 3 weeks had an ORR of 19% and median OS of 8 months [62]. Camerini et al. concluded that oral vinorelbine is a valid option in this selected population. Metronomic vinorelbine in elderly patients with advanced NSCLC is considered in the next section [63].

The 2014 NCCN recommendations suggest that platinum-based combinations and single agent therapy are both reasonable alternatives in the elderly [64]. Fit older patients, like their younger counterparts, benefit from platinum-based doublets, though carboplatin is preferred to cisplatin. For unfit older patients, single agent vinorelbine or gemcitabine may be used. If vinorelbine is chosen, the oral schedule is an alternative.

5. Metronomic therapy

Metronomic therapy involves the long-term, frequent administration of cytotoxics at far below the maximum tolerated dose but with no drug-free periods. One rationale is that cytotoxics can be antiangiogenic in preclinical models [65] and the approach has attracted attention because of possible synergy with molecularly-targeted agents such as bevacizumab.

Much interest has centred on low-dose metronomic cyclophosphamide. This is regarded as promising despite the fact that studies to date have involved heterogeneous regimens and were generally small and non-randomised [66]. The dose per day ranges from 25 to 100 mg, but 50 mg is the most frequent. Studies involving metronomic cyclophosphamide, capcitabine and vinorelbine are shown in Table 3.
There is also an additional context in which metronomic therapy may have specific value. In low and middle-income countries where hospital-based care is limited, “constraint-adapted” management providing metronomic treatment that is relatively inexpensive, well tolerated and easy to access offers the prospect of disease control that is otherwise absent [74].

6. Discussion

Whereas combination chemotherapy is the standard of care in advanced NSCLC and CRC, in breast cancer single agent capecitabine and vinorelbine are standard treatments. This is the case in the old, but also in young and fit patients with minimally symptomatic, slowly progressive disease [28]. An advantage of oral vinorelbine and capecitabine in relation to other single agents, notably the taxanes, is a favourable safety profile and the absence of alopecia. Due to its toxicity profile and reasonable efficacy, metronomic therapy represents a treatment option for older patients with several different tumour types who are unsuited to or refuse standard chemotherapy. At the very least, the availability of oral agents provides additional choice to patients; and there is some evidence that – other things being equal – patients prefer the oral route [11]. However, in the US, costs of oral therapy may be significant and lead to issues concerning access to treatment [75].

In the context of oral agents in general and of cytotoxics in particular, it is also important to recognise that compliance is an issue. This is especially true in older patients who may be more prone to lapses in memory and episodes of confusion than their younger counterparts. Oral agents would not be appropriate where such problems exist. And we know, for example, that frailty at baseline increases the chances that elderly breast cancer patients prescribed adjuvant hormonal therapy will fail to start treatment or discontinue [76].

In itself, age should not prevent access to treatment that is potentially curative or that increases the duration or quality of life [27,48]. However, age is undoubtedly a relevant factor when making treatment decisions. A shorter life expectancy needs to be taken into account when weighing likely benefits against toxicity. Comorbidities are more frequent, complicating treatment and adding to its risk, and – irrespective of concomitant disease – there is age-related (though by no means uniform) decline in renal and cardiac function.

In a study of almost 10,000 people aged 65 years and older in long-term residential care, Garg et al. found that 17% of men and 14% of women had a serum creatinine level above the upper limit of normal [77]. And it should also be noted that many patients, particularly the old, have abnormal renal function even with normal creatinine [78,79].

A prospective study of 562 patients aged 70 and over who were about to start chemotherapy found that serious toxicity (i.e. grade 4 haematologic or grade 3–4 non-haematologic events) occurred in 64% [80]. However, the purpose of this study was not simply to document the frequency of toxicity but to predict it. In addition to the inherent toxicity of the chemotherapy regimen, authors identified a series of patient-based factors (biochemical, physiological and psychological) which enabled calculation of a “CRASH” (Chemotherapy Risk Assessment Scale for High-Age patients) score which predicted risk of severe toxicity among elderly cancer patients. The work of Hurria et al. in predicting chemotherapy toxicity has also contributed to the development of clinical trials in older patients [81]. Such scoring systems have still to enter regular use. However, everyday practice involves judgements made along similar lines. Among the many factors influencing treatment decisions are the extent of physical and mental frailty, life expectancy, the likely risks and benefits of treatment, whether treatment is curative or palliative in intent, the patient’s ability to tolerate treatment and possible PK changes due to age and drug interactions. When self-prescribed alternative and complementary medicines are included, older cancer patients may be taking nine different medications [82]. Above all, patient preference should be decisive in determining therapy. The latter is especially important when quality of life is the main issue, and patient preferences are not always well understood by family and carers [4].

The disparity in age and comorbidity between patients in clinical trials and those seen by oncologists and geriatricians in everyday practice is profound. Hence there is little guidance on optimum treatment. However, the evidence we have suggests outcomes for fit older cancer patients are similar to those for younger patients [27,48]. Among those who are less fit or who have greater difficulty accessing hospital services, oral alternatives to i.v. chemotherapy should be explored. There is no morbidity associated with long term central venous access, and treatment with oral agents may be easier to tolerate. Possible disadvantages include the fact that compliance is not assured, with potential implications for reduced efficacy.

Conflict of interest statement

Demetris Papamichael has been on Roche Advisory Board meetings and has been given invited lectures for Roche.

Matti Aapro is a consultant for Amgen, BMS, Celgene, GSK, Helsinn, JnJ, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Teva, Vifor. He has received honoraria for lectures at symposia of Amgen, Bayer Schering, Cephalon, Chugai, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Teva, Vifor.
Elizabeth Quoix has been on Roche, Astra, Genentech, Pfizer and Amgen advisory board meetings and has received travel grants for meetings and congresses from Pfizer, Lilly and Roche.

Laura Biganzoli has been a consultant for Roche.

Stuart Lichtman, Jean-Pierre Michel and Christine Walko, declared no conflict of interest.

Funding

This work was supported by an unrestricted grant from Roche.

Acknowledgement

Rob Stepney (medical writer, Charlbury, UK), was rapporteur at the Paris meeting, prepared an initial draft of this paper, and edited subsequent drafts.

References


[72] Barber EL, Zsiros E, Lurain JR, et al. The combination of intravenous bevacizumab and metronomic oral cyclophosphamide is an effective regimen for platinum-resistant recurrent ovarian cancer. J Gynecol Oncol 2013;24:258–64.


