Anti-Tumour Treatment

Taxanes in the treatment of breast cancer: Have we better defined their role in older patients? A position paper from a SIOG Task Force

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ARTICLE INFO

Article history:
Received 1 October 2015
Received in revised form 24 November 2015
Accepted 25 November 2015

Keywords:
Breast cancer
Elderly
Docetaxel
Paclitaxel
Nab-paclitaxel
Taxanes

ABSTRACT

Along with anthracyclines, taxanes are the most active cytotoxic agents in breast cancer (BC). Balancing efficacy against toxicity in older patients with reduced physiological reserves and significant comorbidities is both important and difficult. This is especially so given the under-representation of elderly patients in major trials and a consequent lack of evidence for drug, dose and schedule. However, BC is frequent in elderly women, who are a growing proportion of the population. Careful consideration of their care is therefore imperative. Treatment that can cure or extend the duration and quality of life should not be restricted by age, but needs to be tailored to the circumstances of elderly patients. In adjuvant use, taxane toxicity in older women is greater than in their younger counterparts, limiting its sequential combination with anthracyclines for high-risk disease unless patients are in very good health. More frequently taxanes are used alone (weekly paclitaxel, three-weekly docetaxel) or combined with cytotoxics other than anthracyclines (e.g. docetaxel plus cyclophosphamide) to reduce cardiac risk, especially in HER-2-positive patients who may develop additional trastuzumab-related cardiac events. In elderly patients with metastases, weekly paclitaxel and three-weekly docetaxel are among the cornerstones of treatment, with generally acceptable toxicity. Three-weekly docetaxel at the approved dose of 100 mg/m² is not appropriate for the elderly. Nab-paclitaxel has efficacy comparable with solvent-based taxanes without need for steroid premedication but has been little studied in older BC patients. A head-to-head comparison with weekly paclitaxel favoured the solvent-free formulation for pathologic response, but those studied were a general adult population. Compared with early stage disease, choice of taxane and regimen in the metastatic setting relies even more on availability and preferences with regard to schedule, toxicity profile and cost, especially for recently developed formulations.

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Introduction

The median age at diagnosis of breast cancer (BC) is 61 years, 41% of cases occur in women aged 65 and over, and 21% of new diagnoses are in women aged over 75 [1]. The median age of those who die of the disease is 68. BC is in large part a disease of the elderly [2]. Breast cancers in the elderly are more likely to be indolent than in younger women, and the prevalence of hormone receptor-positive and HER2-negative tumours is higher. Yet the risk of dying from BC increases with age [3], despite the greater contribution from competing causes of mortality.

A probable explanation is that age strongly affects the treatment received. Elderly patients are less likely than their younger counterparts to have full diagnostic assessment and post-operative radiotherapy [4]. And they are less likely to be treated with full courses of chemotherapy of proven efficacy. Hence increasing age is not only a risk factor for the development of breast cancer but also for its undertreatment [5]. Geriatric assessment, preceded if necessary by a short geriatric screening test, can contribute to evaluation of the general health status of cancer patients and leads to therapy that is more adapted to individual needs. Such assessment is feasible, reveals previously unknown problems, and potentially influences treatment decisions. General
issues concerning management of the older cancer patient, including the role of geriatric assessment, are considered elsewhere [6,7].

One reason for undertreatment may be the underestimation of patients’ fitness and their life expectancy if free from cancer. In fact, the median life expectancy of a seventy year old woman is fifteen years, and ten years at the age of eighty [8]. Another reason is uncertainty about the efficacy of treatment since older patients are substantially underrepresented in clinical trials [9]. For example, only 16% of patients enrolled in the pivotal trials of adjuvant trastuzumab were aged 60 years or older [10,11].

Even when the results of major trials are aggregated, data may be insufficient to arrive at clear conclusions regarding the elderly. Thus, in the most recent meta-analysis, the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) assessed the long-term outcome of 100,000 women included in more than a hundred randomised trials [12]. In studies that had involved taxane or anthracycline-based regimens, the proportional reductions in risk of recurrence or death from breast cancer were little affected by age. Again, relatively few women aged over 70 were enrolled. The EBCTCG concluded that elderly women appeared to have experienced as great a benefit in recurrence and mortality risk as younger patients, based on relative risk reduction. However, absolute gain – the goal that is understood and sought by patients – may be quite different.

Although still providing a statistically significant reduction in relative risk, chemotherapy would very likely be declined by most elderly patients with a T1 N0 breast tumour since the 1–2% absolute additional benefit brought by the addition of chemotherapy to endocrine therapy – while it should be discussed – would not justify the likely impact on functional status and independence.

In part, this goes against epidemiological and population-based research suggesting that, even when data are adjusted for stage of disease, the wider population of older women with BC has benefited less than younger women from survival improvements due to recent advances in treatment. This is true both for Europe [13] and in the United States [14]. In the USA, incidence-based mortality rates among women aged less than 70 years fell 38% between 1990 and 2003 for those with ER-positive tumours. For those with ER-negative tumours, the mortality reduction was 19%. However, for women aged 70 and over with ER-positive tumours the mortality reduction was only 14%; and older women with ER-negative tumours showed no decline in mortality over the relevant period. Jatoi et al. concluded that we need increased efforts to improve outcome in the elderly.

General aspects of this problem have been addressed by the National Comprehensive Cancer Network [9] and in joint recommendations from the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) [15,16]. The present paper has a more specific remit: consideration of the potential that taxanes have to improve the balance of efficacy versus toxicity in the elderly breast cancer patient.

Older breast cancer patients: general considerations

In contrast to chronological ageing, biological ageing is not uniform. Cancer patients aged 75 can be as fit as those decades younger, and as eager to maximize their chances of long-term survival. At the age of 75, a breast cancer patient who was otherwise in good health would have a life expectancy of over ten years [17].

However, there is no doubt that aging is associated in many patients with decreased physiological reserves and altered pharmacokinetics which may reduce the tolerability of cytotoxic chemotherapy and enhance the risk of treatment-related adverse events (AEs) [18,19]. There is also a clear increase in the likelihood of comorbidities such as cardiovascular disease and diabetes. This is evident, for example, when data from the ATHENA study in metastatic breast cancer (MBC) are analysed by age: active hypertension was evident in 49% of patients aged 70 or above but in only 20% of those who were younger; and diabetes had been diagnosed in 11% of the older group, but in only 5% of younger patients [20]. The increased frequency of comorbidities was reflected in baseline medication and, as a consequence, a greater risk of drug interactions. These considerations require a practical and individualized approach to therapy based on comprehensive geriatric assessment (CGA) including both physical and cognitive function and the availability of social support.

One important aspect of treating elderly BC patients is the increased risk of anthracycline-induced cardiotoxicity. According to a retrospective review of data from 630 patients involved in three phase III studies (two in BC), exposure to a cumulative dose of 550 mg/m² doxorubicin was associated with a cumulative 26% risk of drug-related congestive heart failure (CHF) [21]. Independent of performance status and comorbidities, older age increased the risk of cardiotoxicity. Moreover, data from more than forty thousand women aged 66–80 years show that CHF induced by anthracyclines occurs at a steady rate up to ten years after exposure in the adjuvant context. At ten years, the CHF rate among women who had had no adjuvant chemotherapy was 29%. The figure among women with non-anthracycline chemotherapy was 32.5%, while 38.4% of women who had been treated with anthracyclines had had a diagnosis of CHF [22]. This has led to calls for cardiac risk factors to be more effectively identified prior to treatment, for more rigorous monitoring of cardiac function, for protocols that encourage early intervention when likely problems are identified, and for the consideration of potentially less cardiotoxic anthracycline formulations or agents [23]. In this context, there is interest in using taxanes instead of anthracyclines since cardiac toxicity is generally not an issue.

Taxanes in the elderly

Along with anthracyclines, taxanes are the most effective agents in BC. They are inhibitors of microtubule dynamics, and the two leading compounds are solvent-based. Both are associated with major toxicities such as myelosuppression and neuropathy which may restrict their use, particularly in elderly patients; and the need for steroid premedication hinders their use in patients with diabetes. Other less threatening side-effects can adversely affect patients, particularly the elderly, who are more concerned about quality than quantity of life. For example, despite use of the cold cap, alopecia remains psychosocially damaging, especially with docetaxel [24]. Our knowledge about optimal drug, dose and schedule in older women with BC is limited since relatively few such patients have been included in key trials and data are not generally analyzed by age. Nevertheless reviews in 2004 and 2009 considered whether docetaxel and paclitaxel (in standard formulations) could be used in a way that maximized their therapeutic index [25,26].

Pharmacokinetics

Of particular relevance to the pharmacokinetics (PK) of taxanes in the elderly are the potential for patients to be hypoalbuminaemic, which may increase the concentration of highly protein-bound drugs, and decreased cytochrome P450 activity in the ageing liver, which may limit their metabolism. In relation to the toxicity of three-weekly (q3w) docetaxel, data suggest that the increased risk of febrile neutropenia with age (16% in patients 65 years old or older compared with 0% in their younger counterparts) is not
due to altered PK but to increased bone marrow sensitivity [27]. This view is supported by the study of Minami et al. in non-small cell lung cancer [28]. Data are less clear for paclitaxel for which there is great inter-patient variability in clearance [29]. Moreover clearance of its unbound form is less in patients older than 70 years, although this seems to have no impact on rates of neutropenia [30].

The potential importance of schedule

Overall, studies of docetaxel and paclitaxel do not suggest the need for dose modification for reasons of age alone. In the case of docetaxel, this applies only to the 75 mg/m² q3w dose and schedule used in lung, prostate and some breast regimens. Of note, with rates of febrile neutropenia often approximating 15–20%, this 75 mg/m² dose requires primary prophylaxis with granulocyte-colony stimulating factor [31]. Much greater prudence is warranted with the higher 100 mg/m² dose used in some common adjuvant chemotherapy schedules. Although approved and considered standard for adults in many European countries, this dose is difficult to administer to the majority of older patients.

In the 2000s, the concept of dose-density and attempts to circumvent side-effects that were reported to be peak-dependent led to the development of weekly schedules. Biganzoli et al. reviewed four randomized trials of weekly vs q3w taxanes in BC [26]: two studies involved docetaxel in metastatic breast cancer (MBC), [32,33] one paclitaxel in MBC, [34] and one docetaxel and paclitaxel as alternatives following standard adjuvant doxorubicin plus cyclophosphamide [35].

Taking the studies overall, data suggest that weekly paclitaxel has a better haematological safety profile, although this schedule is associated with an increased incidence of neuropathy both in advanced stages [34] and early stages [35]. Weekly paclitaxel also seems more effective in both the adjuvant and metastatic settings and represents the recommended schedule also in the elderly. Strict monitoring of neurotoxicity is recommended this group. Weekly docetaxel might be less myelosuppressive than q3w administration, but non-haematological complications and poor adherence can be frequent, and weekly docetaxel in the adjuvant setting is less effective than three-weekly administration [36]. Hence this schedule is little used.

The trials considered above were not confined to elderly patients. However, based on the suggestion that weekly scheduling might improve the balance of benefit versus toxicity, several subsequent studies of weekly taxanes were conducted specifically in older women with BC.

Hainsworth et al. investigated weekly docetaxel in elderly BC patients with advanced disease [37]. Patients with a median age of 74 years and median PS of 1 received 36 mg/m² docetaxel for six weeks followed by two weeks off. Severe neutropenia occurred in only 0.4% of 448 courses but cumulative fatigue (which was related to total dose administered) led to treatment discontinuation in nine of 41 patients.

The French Unicancer GERICO group investigated an alternative biweekly docetaxel regimen (50 mg/m² q2w) in women at least 70 years old with MBC [38]. This regimen was not feasible: after inclusion of 27 patients, there was an unacceptably high rate of fatal events, potentially related to increased steroid-induced immunodeficiency.

The most important safety data published so far using such a weekly docetaxel schedule in the elderly come from the recently published Italian ELDA phase III trial. In comparison with standard CMF (cyclophosphamide, methotrexate and 5-fluorouracil), weekly docetaxel caused less haematological toxicity, nausea and mucositis; but allergy, fatigue, hair loss, onychopathy, dysgeusia, diarrhoea, abdominal pain, neuropathy, cardiac and skin toxicity were worse, and there was no difference in outcome [39]. The occurrence of fatal events in ELDA feeds the debate about taxanes being aggressive cytotoxics, irrespective of schedule.

In relation to weekly paclitaxel in BC, three trials (all of weekly 80 mg/m² and all in metastatic or advanced disease) provide relevant data [40–42]. In the Perez et al. study, grade 3–4 neutropenia occurred in 15% of patients aged 65 years or older, which was the same proportion as in younger patients. In the study by ten Tije et al. weekly paclitaxel was again relatively well tolerated, but 32% of patients discontinued because of fatigue. In the Del Mastro study, cardiotoxicity emerged as an unexpected problem, and this did not seem to be related to prior exposure to anthracyclines. However the majority of data in the adult population do not suggest that weekly paclitaxel is associated with cardiac failure.

In relation specifically to the elderly or frail, Beuselinck et al. carried out a randomized phase II trial of weekly paclitaxel vs weekly docetaxel in 70 metastatic BC patients considered unsuited to q3w regimens, including 28 aged ≥ 70 [43]. Median OS was longer with paclitaxel (56 vs 32 weeks). Anaemia and neurotoxicity were more frequent with paclitaxel and oedema and fatigue more frequent with docetaxel, though the incidence of grade 3 or greater toxicity was never higher than 10%. Weekly administration of both drugs was considered tolerable in these less fit patients. This relatively recent study therefore supported the conclusion of an earlier review that weekly taxanes are a reasonable option for older patients with BC [25].

Other compounds

Toxicity issues with the two main taxanes have led to the search for other formulations, especially those, such as albumin-bound paclitaxel (nab-paclitaxel), which might avoid need for the allergenic solvent vehicle Cremophor EL [44,45]. Such formulation might also have the advantage of faster clearance compared with solvent based agents, as shown in a randomized crossover pharmacokinetic study [46]. Good tolerability across age groups has been reported [47]. Other initiatives include the use of a cationic liposome-encapsulated formulation for paclitaxel. This has promising preliminary activity and allows targeting of tumour endothelium, but the issue of hypersensitivity reactions would need to be resolved [48].

Although cabazitaxel has not been investigated in depth in BC, results were encouraging with a weekly schedule in relatively unfit metastatic, castration-resistant prostate cancer patients progressing after docetaxel. There were no serious safety concerns [49,50]. Given potential clinical and pharmacokinetic advantages over its predecessor, docetaxel, these phase II data would support its investigation also in elderly BC patients.

Taxanes according to setting

Metastatic disease

Among available options for MBC, selection of the most appropriate in an individual case should take into account both the likelihood of meaningful response and the risk of specific AEs. The SIOG-EUSOMA guidelines suggest that older MBC patients benefit from chemotherapy to much the same extent as younger patients [16]. Single-agent chemotherapy is generally preferred to combination regimens since polychemotherapy is usually more toxic and provides, at most, limited survival gain. Preference should be given to chemotherapy agents and schedules with better safety profiles.

These considerations apply to taxanes for elderly patients. As in younger patients, weekly paclitaxel is one of the most widely used...
MBC regimens. Docetaxel can also be used either weekly or q3w, although more often with the standard q3w schedule, and preferably not at the high 100 mg/m² dose. One of the main issues is the need to avoid non-haematological toxicities such as neurotoxicity, which is clinically significant from grade 2 and can jeopardize the functional status central to care of the elderly.

In a combined analysis of two Cancer and Leukemia Group B (CALGB) studies (9324 and 9840), Lichtman et al. found that women over 65 years receiving paclitaxel as either first- or second-line therapy for MBC were no less likely than their younger counterparts to experience tumour response and survival benefit [51]. However, elderly patients in the second-line setting were considerably more likely than younger women to experience grade ≥ 3 neurotoxicity.

The impact of specific AEs such as sensory neuropathy will vary from one woman to another and it may be helpful to assess their impact on function using the Instrumental Activities of Daily Living (IADL) or Activities of Daily Living (ADL) scales and to monitor patients closely while they are on treatment [52]. The fatigue commonly associated with weekly docetaxel has a particularly negative impact on functioning in older patients [53]. Treatment with conventional solvent-based taxanes (weekly paclitaxel or q3w docetaxel) is likely to be feasible in the majority of elderly patients with MBC, provided that function is closely monitored.

Nab-paclitaxel might prove to be both a practical and effective alternative to standard taxanes [54]. In a randomized phase III study comparing 3 weekly paclitaxel with 3 weekly nab-paclitaxel, response rate (RR) and progression-free survival (PFS) were significantly higher with nab-paclitaxel [45]. In a randomized phase II study comparing q3w docetaxel, q3w nab-paclitaxel and two doses of weekly nab-paclitaxel (given over three of four weeks), PFS was significantly longer with weekly 150 mg/m² nab-paclitaxel than with docetaxel 100 mg/m² [12.9 vs 7.5 months]. The incidence of grade 3 neuropathy was higher with 3 weekly nab-paclitaxel than with standard paclitaxel in the first study [45] and similar with the two agents in the second one [55]. It is worth noting that the median time to resolution of grade 3 neuropathy to a lesser grade was shorter with nab-paclitaxel than with the conventional taxanes [45,55].

In MBC, there is no comparison between single-agent weekly nab-paclitaxel and weekly paclitaxel. The single head-to-head comparison we have favours the solvent-free formulation, but this is in the neoadjuvant setting, in the general adult population, and based on pathologic response [56]. Of note, the recently published CALGB 40502/NCCTG N063H (Alliance) phase III trial compared single agent weekly (3 or 4 weeks) nab-paclitaxel 150 mg/m² or ixabepilone 16 mg/m² versus paclitaxel 90 mg/m², but with the addition of bevacizumab, which is known to have an impact on toxicity [57]. The arm with the semisynthetic analogue of epothilone B yielded a PFS benefit inferior to paclitaxel, while the nab-paclitaxel arm was not superior. The addition of bevacizumab hinders the interpretation of safety data especially given the high doses used weekly in the two experimental arms. Haematological toxicity was higher with nab-paclitaxel. Although statistically different across arms, grade ≥ 2 neuropathy was frequent in all (range 46–54%), and relative dose intensity disadvantaged nab-paclitaxel with higher discontinuation and dose reduction rates.

No study has prospectively evaluated nab-paclitaxel in the older MBC population and this makes it even more difficult to draw any firm conclusion for elderly patients. However, the single post hoc analysis of patients aged 65 and over enrolled in the first two MBC trials [45,55] suggests that weekly nab-paclitaxel is safe, effective and appropriate first-line therapy [58].

Prospective trials focused on elderly patients are needed to better define the role and optimal dose of nab-paclitaxel in this population. The current EFFECT trial is investigating weekly 100 vs 125 mg/m² for breast cancer patients aged 65 and above [59]. Preliminary data in 44 patients suggest that both doses can safely be administered to elderly patients. The most frequently reported adverse events are fatigue and neurotoxicity, and only one patient to date has experienced grade 4 non-haematological toxicity. The primary composite endpoint combines progressive disease or death and functional decline monitored every cycle by ADL and IADL. This reflects the SIOG and EORTC recommendations regarding the methodology of clinical trials in elderly patients [60]. As a general comment, nab-paclitaxel might be an alternative in this setting, especially in patients in whom there is concern about allergic reactions and/or use of steroids.

Early stage breast cancer

The NCCN Task Force on BC in the older woman concluded that there is no clear preference for any particular adjuvant regimen. But they suggested caution with anthracyclines; use of less myelosuppressive therapies; careful evaluation of renal and hepatic function; possible benefits of weekly dosing; and early use of myeloid growth factors [9].

Certain trials which enrolled predominantly younger women include sufficient elderly patients to allow subgroup analyses by age. However, exclusion criteria other than age mean that the older patients enrolled were more fit than the wider population of older women with BC. Even so, Muss et al. showed increased haematological toxicity and treatment-related deaths among older patients in the CALGB trials [61]. Adjuvant regimens that are considered standard in young patients are not always well tolerated by the elderly. However, the attempt to provide a less toxic alternative, eg by using capecitabine, illustrates the potential trade-off between tolerability and efficacy. The survival benefit of standard doxorubicin plus cyclophosphamide (AC) or CMF was greater than with oral capecitabine (3-year OS 91% vs 86%) in a selected population of older patients with stage I-IIIB breast cancer [62]. The ICE-1 study also suggested that adjuvant capecitabine has no role: capecitabine compared against no chemotherapy in patients receiving ibandronate found no difference in PFS or OS [63].

Might taxanes be helpful in elderly EBC?

Jones et al. were the first to report the potential benefit of adjuvant taxanes in elderly patients (≥ 65 years), based on the unplanned sub-group analysis of the 9735 trial which compared a non-anthracycline regimen of docetaxel plus cyclophosphamide (TC) versus AC [64]. At seven years, both younger and older patients assigned to TC (N = 428 and 78 respectively) were more likely to be free of disease than those assigned to AC. Both age groups also showed an OS advantage for TC. Elderly women were more likely to experience febrile neutropenia (FN) with TC than with AC (8% vs 4%). The corresponding figures in younger patients were 4% and 2%. However, it was unclear how many patients received prophylactic oral antibiotics and/or G-CSF. In the elderly cohort, grade 3–4 anaemia was more common with AC than TC (5% vs <1%). The three late deaths without relapse all occurred in the AC group. The authors concluded that these data supported increased use of the non-anthracycline regimen in older women, especially those with lower risk disease.

To further document TC in elderly women, Freyer et al. reported a retrospective study of 110 women aged over 70 who had completed TC, the majority receiving 75 mg/m² docetaxel and 600 mg/m² cyclophosphamide [65]. Seventy-one percent had at least one comorbidity at diagnosis. During treatment, 5% of patients had FN and the rate of grade 3–4 non-haematological toxicities was 5% or less. G-CSF had been given as primary prophylaxis in 52% of patients. In these circumstances, Freyer et al. regard TC as
a safe regimen for BC patients aged over 70 but suggest that clinical trials are required to further evaluate adjuvant taxanes in the elderly.

However the true rate of FN with TC in the elderly is debated. Younus et al. reviewed the records of 134 patients (median age 62) and concluded that adjuvant TC in community practice causes a much higher rate of FN (20%) than is suggested by the trial literature [66]. Forty percent of patients in this series were 65 or older, and their risk of FN was 26%. These data strongly support primary prophylaxis with G-CSF when using TC in the elderly, in agreement with EORTC guidelines, where the FN risk is either greater than 20% or between 10% and 20% in the presence of other risk factors including age of 65 years and above [31].

In the ELDA trial, safety profiles differed between CMF and weekly docetaxel, but DFS and OS were similar in the two groups [39]. Quality of life was worse with docetaxel, as were most non-haematological side effects. Age, functional impairment, number of comorbidities and docetaxel treatment were independently associated with severe non-haematological toxicity in this population aged 65–79 years. Based on docetaxel's safety profile, negative impact on QoL and the absence of superior efficacy over standard CMF, weekly docetaxel cannot be considered a standard adjuvant regimen in older breast cancer patients [39,66,67].

Fewer data are available for adjuvant paclitaxel in the elderly. Single agent paclitaxel was compared with AC in CALGB 40101 [68]. Paclitaxel was less toxic but the trial did not show non-inferiority to AC: single-agent paclitaxel has not superseded AC. Patients treated with standard q3w or dose-dense q2w paclitaxel greatly exceeded those treated with the optimal weekly schedule. Outcome using this more attractive schedule therefore remains unclear, especially for elderly patients.

Helpful information can be derived from combined data analyses that allow extraction of data dealing specifically with the elderly. Loibl et al. assessed data from more than four thousand patients in four randomised studies of anthracycline and taxane-containing chemotherapy between 1999 and 2005 (two in the adjuvant setting and two neoadjuvant) [69]. Treatment variables and toxicity were analysed by age: 3160 patients were less than 60 years old, 645 were aged 60–64 years, and 422 were 65 and over. In the latter group, the median age was 67.

Dose delays and reductions and discontinuation of treatment increased with age. Thus, among patients aged under 60, 9% had dose reductions, compared with 14% of those aged 65 and over. Treatment discontinuation occurred in 12% vs 19%. Grade 3–4 neutropenia affected 47% of patients under 60 but 57% of patients who were 65 and over. However, the risk of FN showed little increase with age. Older patients were more likely than their younger counterparts to experience fatigue and gastrointestinal AEs.

Loibl et al. conclude that (neo)adjuvant chemotherapy in the elderly is feasible in patients eligible for an anthracycline/taxane regimen, that its toxicity can be reduced by sequential administration of anthracyclines and taxanes and by prophylactic treatment, and that weekly paclitaxel may be preferable to docetaxel in a sequential anthracycline/taxane regimen.

In addition to these studies favouring weekly paclitaxel, relevant data come from Barcanes et al. who used the SEER/Texas Cancer Registry-Medicare database to compare the risk of hospitalization in patients with early-stage BC who received different chemotherapeutic regimens [70]. Among patients older than 65 years, AC and TAC (but not dose-dense AC plus paclitaxel) were associated with a higher risk of hospitalization than TC.

Following promising results with nab-paclitaxel in MBC, the ICE II study compared investigators' choice of epirubicin plus cyclophosphamide or CMF versus weekly nab-paclitaxel plus capecitabine in 400 non-frail elderly patients at increased risk of relapse [71]. Although not the primary endpoint of the trial (which focused on safety), rates of invasive disease-free survival were equivalent between the treatments at 48 months. In the experimental arm, grade 3–4 toxicity was significantly more frequent (59% vs 19%) and fewer patients completed treatment (65% vs 93%). Haematological toxicity was more frequent with EC/CMF and non-haematological toxicity more frequent with nab-paclitaxel plus capecitabine. In the context of the elderly, the important feature of this study was that the largest influence on tolerability was the regimen used, and not comorbidity, albumin and status on geriatric assessment.

This lack of conclusive data for the elderly population might be resolved by the ongoing WAFE trial comparing single agent nab-paclitaxel against epirubicin in women with early BC who are elderly or unfit for a three-weekly polychemotherapy regimen.

**Taxanes in HER2-positive disease**

HER2-positive (HER2+) disease must be considered separately. The addition of trastuzumab to chemotherapy has dramatically improved outcome in BC, both in metastatic and adjuvant settings. However, this has been at the cost of increased cardiotoxicity. This is perhaps less of an issue in MBC where many non-cardiotoxic cytotoxics are available for combination with trastuzumab. However, more caution is needed in the adjuvant setting where age is a proven risk factor for trastuzumab cardiotoxicity and options are limited [72–75]. Use of an anthracycline-free regimen could be important in older patients with low-intermediate risk of relapse or who present with comorbidities that could increase cardiotoxicity.

In an open-label phase II study, predominantly in node-negative patients, the non-anthracycline TC combination with trastuzumab achieved a two-year DFS of 97.8% (95% CI 96.0–98.8) and overall survival of 99.2% (95% CI 97.8–99.7) [76]. Cardiac dysfunction was seen in only 6% of patients and was generally reversible. Although the median age of patients entered was 55 years, women as old as 75 were included.

The regimen of docetaxel plus carboplatin plus trastuzumab (TCH) must also be considered for elderly patients since it too does not contain anthracyclines. Efficacy is similar to standard anthracycline-taxane regimens while cardiac toxicity is considerably less [77]. However, the study had an upper age cut-off of 70 years, so there are no data in truly elderly patients. Although theoretically adjusted to renal function, the high dose of carboplatin (AUC 6) in combination with docetaxel would probably make this schedule difficult for the majority of older patients.

The combination of weekly paclitaxel and trastuzumab in node-negative HER2+ disease has also been studied [78]. Although this was a single-arm phase II with no specific focus on the elderly population, the relapse rate was encouraging low (three-year DFS 98.7%), and the combination relatively non-toxic. Among 406 patients entered, there have been two cases of symptomatic CHF. Weekly paclitaxel and trastuzumab might therefore be a potentially valuable regimen in stage I elderly patients or in elderly patients not considered candidates for polychemotherapy.

**Discussion and recommendations**

Although BC is the leading cause of cancer death in women, although risk of the disease increases with age, and although the proportion of the population over 65 years of age is rapidly expanding, few randomized controlled trials (RCTs) have systematically investigated treatment options in older BC patients; and older women are substantially under-represented in registration studies.
Table 1
SIoG Task-force recommendations on the use of taxanes in elderly breast cancer according to setting and tumour biology.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Regimen</th>
<th>Evidence in the elderly</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Adjuvant HER2-negative</td>
<td>A/E-based (3–4 cycles) → taxane (3–4 cycles)</td>
<td>Sub-group analyses</td>
<td>Only fit and high-risk patients; caution about cardiotoxicity and haematotoxicity; primary prophylactic G-CSF for anthracycline part (and docetaxel 3 weekly if that taxane is chosen)</td>
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<td></td>
<td>AC/EC × 4</td>
<td>Prospective studies</td>
<td>Feasible in the standard elderly population with caution about cardiotoxicity; primary prophylactic G-CSF</td>
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<tr>
<td></td>
<td>CMF × 6</td>
<td>Prospective studies</td>
<td>Feasible in the standard elderly population with caution about haematotoxicity and compliance</td>
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<td></td>
<td>TC × 4</td>
<td>Sub-group analyses</td>
<td>Feasible in the standard elderly population with primary prophylactic G-CSF</td>
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<tr>
<td></td>
<td>Weekly docetaxel</td>
<td>Prospective study</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Weekly paclitaxel</td>
<td>No evidence</td>
<td>But may be considered in patients who are not candidates for poly-chemotherapy such as TC</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>Nab-paclitaxel plus capecitabine</td>
<td>Prospective study</td>
<td>Not recommended</td>
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<td></td>
<td>A/E-based (3–4 cycles) → taxane (3–4 cycles) + trastuzumab</td>
<td>Sub-group analyses</td>
<td>Only fit and high-risk patients; caution about cardiotoxicity and haematotoxicity; primary prophylactic G-CSF for anthracycline part (and docetaxel 3 weekly if that taxane is chosen)</td>
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<td>TCH (C = capecitabine) × 6</td>
<td>No</td>
<td>Concern about toxicity</td>
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<tr>
<td></td>
<td>TC × 4 + trastuzumab</td>
<td>No</td>
<td>Feasible in the standard elderly population with primary prophylactic G-CSF, especially in presence of risk factors for cardiotoxicity</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Weekly paclitaxel (3 months) + trastuzumab</td>
<td>No evidence</td>
<td>But may be considered in elderly patients who are not candidates for poly-chemotherapy such as TC</td>
</tr>
<tr>
<td></td>
<td>Weekly paclitaxel</td>
<td>Prospective study</td>
<td>Feasible</td>
</tr>
<tr>
<td></td>
<td>Docetaxel q3w</td>
<td>Sub-group analyses</td>
<td>Feasible</td>
</tr>
<tr>
<td></td>
<td>Weekly docetaxel</td>
<td>Prospective study</td>
<td>Feasible</td>
</tr>
<tr>
<td></td>
<td>Nab-paclitaxel</td>
<td>Sub-group analyses</td>
<td>Feasible</td>
</tr>
</tbody>
</table>

**A** = doxorubicin, **E** = epirubicin, **C** = cyclophosphamide, **G-CSF** = Granulocyte Colony Stimulating Factor, **M** = methotrexate, **F** = 5-fluorouracil, **T** = docetaxel, **H** = trastuzumab.

* EORTC guidelines for the palliative setting recommend using G-CSF only if there are no similarly effective regimens not requiring G-CSF.

Level I evidence is therefore lacking. In its absence, recommendations are based in part on trial evidence that does not achieve the standard of RCTs, on extrapolation from controlled trials in which elderly patients are poorly represented, on subgroup analyses and on clinical experience.

Haematological toxicity may be circumvented by the use of weekly schedules. However peripheral neuropathy remains an important issue irrespective of schedule, reaching up to 40% grade ≥ 2 in the general population. A careful assessment of functionality should be performed, based on the last SIOG update on CGA [7].

Discussing the cost and cost-effectiveness of different therapies is difficult since drug prices vary considerably according to healthcare system, and, even within a single country, may differ from one hospital or insurance provider to another. Within the limits of the health-economic methodologies used, and accepting that healthcare systems differ by country, it has been calculated that nab-paclitaxel is a cost-effective alternative to standard taxanes when the balance between efficacy and the expense of dealing with foreseeable toxicities is taken into account [79–82].

With these caveats, we propose as a summary of the current position the statements shown in Table 1.

**Funding**

This project was made possible by an unrestricted grant from Celgene.

**Conflict of interest**

Laura Biganzoli received a research grant from Celgene for the conduction of an independent clinical trial.

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.

Sibylle Loibl declared no conflict of interest.

HW has received lecture fees, consulting fees and scientific grants that have only been used for scientific purposes, from the following: Amgen, Roche, MMS Belgium, Pfizer US Commercial Operation, Novartis Pharma, Teva Pharmaceuticals Europe, Celgene International, Baxter Belgium.

Etienne Brain declared no conflict of interest.

**Acknowledgements**

Rob Stepney, medical writer (Charlbury, UK), prepared the first draft of this paper and edited subsequent drafts. Dr Stepney has declared that the only remuneration received was from SIOG and that he has no conflicts of interest. We also acknowledge the helpful comments of the SIOG internal review panel: Evandro de Azambuja, Martine Extermann, Gilbert Zulian, Miguel Martin, Alessandro Minisini and Jonas Bergh.

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