Cancer Treatment Reviews 43 (2016) 19–26

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

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

L. Biganzoli [a,*], M. Aapro [b], Sibylle Loibl [c], Hans Wildiers [d], Etienne Brain [e]

[a] Nuovo Ospedale Santo Stefano – Istituto Toscano Tumori, Prato, Italy
[b] Multidisciplinary Oncology Institute, Clinique de Genolier, Switzerland
[c] German Breast Group, Sana-Klinikum Offenbach, Germany
[d] University Hospitals Leuven, Leuven, Belgium
[e] Institut Curie – Hôpital René Huguenin, Saint-Cloud, France

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 cytotoxics 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/m^2 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.

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

* Corresponding author at: Dept of Medical Oncology, Nuovo Ospedale di Prato, Istituto Toscano Tumori, via Suor Niccolina, Infermiera, 20, 59100 Prato, Italy. Tel.: +39 0574 802520.
E-mail addresses: lbiganzoli@usl4.toscana.it, lbiganzoli@uslcentro.toscana.it (L. Biganzoli).

http://dx.doi.org/10.1016/j.ctrv.2015.11.009
0305-7372/

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 more 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/m^2 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