Answers and Remaining Questions Regarding Systemic Treatments for Breast Cancer in the Elderly

a report by

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Currently, nearly half of breast cancer cases occur in women aged 65 and older, and one-third occur in those over age 70. With the growing pace of ageing in the general population of most countries, the incidence in older women may increase by more than 30% over the next decade. Although these numbers may in the future generate financial problems and difficulties in providing adequate care, the oncology community usually fails to appreciate these predictions.

Endocrine Treatments

Late diagnosis and substandard local and systemic therapies are common in elderly breast cancer patients, which is only partially and indirectly 'compensated' by more indolent tumour behaviour due to more favourable biological characteristics. Of these, the higher frequency of tumours expressing oestrogen or progesterone receptors (OR or PgR) makes endocrine treatment an ideal first choice for the majority of elderly breast cancer patients in the metastatic as well as adjuvant setting, assuming the high likelihood of potentially hormone-sensitive tumour status in this population.

The last update of the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group has recently validated these results in adjuvant setting with a high efficacy of tamoxifen preserved in the elderly contrary to chemotherapy. With the arrival of aromatase inhibitors challenging tamoxifen with 5% of extra absolute benefit in reducing the risk of cancer recurrence in post-menopausal women, one might have speculated that the prescription of aromatase inhibitors, upfront or sequentially following tamoxifen, would entirely replace the well-established schedule of an anti-oestrogen given for five years. It is clear that, unlike tamoxifen, aromatase inhibitors are not associated with an increased risk of thromboembolism or uterine cancer. The incidence of fractures and arthralgias is, however, increased among women taking these compounds, and some serious cardiac events have been reported more frequently, for example with letrozole. Unfortunately, data derived from published trials are limited for the elderly population, in whatever setting. Although most of the aromatase inhibitors adjuvant trials allowed inclusion of women without an age limit, the median age is usually around 65, below the 'standard' or 'conventional' 70-year-old threshold, and the proportion of patients over the age of 65–70 represent less than 25–30% of the population. In the largest trial ever conducted in such a post-menopausal population (ATAC), anastrozole was better tolerated than tamoxifen, with fewer serious adverse events. However, the analysis was not done according to age, and no conclusion can be easily drawn among the elderly as a specific subset. In another large trial (MA-17), the benefit conferred by the use of the aromatase inhibitor loses its significance beyond age 60. Although limited, some other data question the potential negative impact of aromatase inhibitors on cognitive functions in relation to the induction of a deep oestrogen deficiency. Thus, added to the challenge of compliance of oral treatments, the available literature precludes drawing any firm conclusions on the advantages and disadvantages of aromatase inhibitors over tamoxifen in the elderly, making longer follow-up with specific subgroup analysis necessary and eagerly awaited.

Despite its 'old age' (as it has been known for more than 30 years), tamoxifen would also benefit from further research given the demonstrated differences in metabolic disposition according to age, including the influence of cytochrome P450 2D6 polymorphism. Another provocative argument consists in challenging data derived from randomised controlled trials, which show a similar impact on efficacy pharmacodynamic end-points (proliferation rate) while decreasing impact on toxic pharmacodynamic end-points (antithrombin III and fibrinogen) when lower doses of tamoxifen are used (1mg or 5mg versus 20mg). Therefore, such a strategy would allow the preservation of optimal anti-tumour action and benefit on bone metabolism, while sparing the most feared side effects.

Chemotherapy and Targeted Treatments

Several groups have suggested that age did not influence response and tolerance to cytotoxic agents. However, the spontaneously narrower therapeutic ratio of chemotherapy is potentially further reduced in the elderly, given the pharmacokinetic and pharmacodynamic modifications induced by ageing, for example end-organ functional declines. Polypharmacy, which is frequently observed with threatening

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drug interactions, worsens the situation. Therefore, whether to use combination or sequential single-agent therapy remains an issue for metastatic breast cancer in the elderly. Sequential therapy often allows optimal delivery of single drugs, potentially reducing the risk of toxicities due to drugs given concomitantly, and often improves quality of life, both of which are key issues for the optimal treatment of elderly patients in the palliative setting.

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Anthracyclines are a central therapeutic option, as an age of more than 65 years is a proven risk factor for developing heart congestive failure beyond a cumulated dose of 400mg/m^2. Leading groups such as the MD Anderson Cancer Centre have published apparently reassuring series showing similar cardiac tolerance to anthracyclines before or after age 65, but often with data derived from highly biased series. Therefore, despite a lack of recommendations on whether to adjust doses of doxorubicin according to age, caution is the rule, and the investigation of less cardiotoxic epirubicin or liposomal forms is warranted.

Other key drugs – such as capecitabine, taxanes, gemcitabine and vinorelbine – have been investigated specifically in the elderly in several trials, usually leading to specific recommendations for adjusted doses.

In the adjuvant setting, the issue of chemotherapy is also a matter for debate, given both the expected long-term benefit and the immediate potential for side effects, which are sometimes life-threatening. For a long time, medical oncologists remained reluctant to prescribe chemotherapy in this setting, since they were short of demonstrative data. For example, the Oxford meta-analysis included the use of adjuvant chemotherapy or anthracyclines in patients over the age of 70 in fewer than 5 and 2%, respectively, out of the 30,000 women included in the database.

Nevertheless, three admirable and recently published retrospective analyses have shaken this uncomfortable position. The Cancer and Leukemia Group B analysis showed the same potential benefit of investigational adjuvant chemotherapy irrespective of age, although there was a higher rate of toxic death – around 5–10 times higher – after age 65 compared with younger patients. Two other series derived from the US Surveillance Epidemiology and End Results registry showed the remarkable potential benefit of adjuvant chemotherapy in the adjuvant setting in patients over the age of 65, but this was confined to the OR-negative population. This was even demonstrated after the age of 70 with the same magnitude of benefit, with around a 25% relative reduction of specific mortality. Thus, these new considerations adequately support the issues raised by two current European trials for OR-negative tumours: the GERICO-06 trial promoted by the French Federation of Cancer Centres and supported by a national grant, which investigates the potential benefit of four cycles of anthracyclines-based chemotherapy (liposomal doxorubicin – Myocet® – and cyclophosphamide), screening tolerance, geriatric scales, quality of life and willingness; and the CASA trial promoted by the International Breast Cancer Study Group, investigating pegylated liposomal doxorubicin (Caelyx®) versus metronomic chemotherapy or abstention in patients over age 65 who are not candidates for standard chemotherapy.

Of note, only one French trial specifically investigating the role of adjuvant chemotherapy with anthracyclines added to hormonotherapy in patients over 65 has been published so far. Despite favourable results, it took 10 years to complete enrolment of roughly 300 patients in this programme, stressing the need to change current mentalities regarding clinical research in the elderly cancer population.

Targeted therapies do not escape questions of discrimination. For example, in the HERA adjuvant trial, fewer than 16% of patients were older than 60. Although the beneficial effect on disease-free survival conferred by the monoclonal antibody was still significant in this strata, the Forrest pilot showed a much looser confidence interval than in younger patients. Furthermore, the recently reported laboratory studies on potential mechanisms for resistance to endocrine therapies that involve crosstalk between growth-factor-signalling pathways and OR open the possibility of combining OR-targeted therapies with growth-factor-targeted inhibitors, and may represent an extraordinarily promising approach for future trials in elderly patients.

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Conclusions

The choice of systemic treatment to propose to an elderly woman with breast cancer should be based on several factors. In the adjuvant setting, the assumed absolute benefit, the patient's life expectancy and anticipated tolerance are key points to consider, as well as the patient's general condition and co-existent diseases. In advanced stages, the choice should focus on tolerance. For younger patients, the promising 'omic' arena will benefit patients irrespective of age. Large national and international collaborative initiatives must be stimulated to answer these emerging questions. Support from public funds is crucial, as in France with the large commitment of the Institut National du Cancer (INCa) with its grants application in order to develop a network of pilot units to co-ordinate research, care, teaching and information in geriatric oncology. ■

For references, see the recent review:
Crivellari D, Aapro M, Leonard R, et al., Breast cancer in the elderly, *J Clin Oncol*, 2007;25:1882–90.

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