Table 1. Meta-analysis of the reduction in odds of relapse and death in postmenopausal women treated with adjuvant tamoxifen and polychemotherapy, EBCTCG 1992 [1]

Age (years)	Tamoxifen Relapse	Tamoxifen Death	Polychemotherapy Relapse	Polychemotherapy Death
50–59	28%	19%	29%	13%
60–69	29%	17%	20%	10%
70+	28%	21%	?	?

Table 2. Benefit and cost-effectiveness of adjuvant chemotherapy in elderly women. Desch and associates [2]

Age (years)	Baseline analysis Months gained	Baseline analysis Cost/QALY	Adjusted for life expectancy Months gained	Adjusted for life expectancy Cost/QALY
60	2.8	$28 200	?	?
65	2.8	$31 300	1.3	$59 300
70	2.2	$36 300	1.0	$75 000
75	1.8	$44 400	0.7	$96 000
80	1.4	$57 100	0.4	$212 500

affect only the risk of first relapse and that the patients did not have severe comorbidity. After carrying out a baseline analysis this was then adjusted for active life expectancy, as shown in Table 2.

In the baseline analysis, there is some small gain (2 months) of life expectancy in those over 70 years of age. However, this was achieved at great cost per quality of life year (QALY). This gain was almost obliterated after adjustment for life expectancy and this led to a significant amplification of cost/QALY. When compared with other procedures with known cost/QALY, this was equal to that of liver transplantation and 12 times the cost/QALY of adjuvant tamoxifen or coronary artery bypass.

This would argue strongly against use of adjuvant chemotherapy for breast cancer in this age group. Furthermore, since chemotherapy has even less adjuvant activity in other solid tumours, it is difficult to assign any role in the elderly.

To demonstrate a cost-effective role for adjuvant chemotherapy in the elderly would be a Herculean task. Suitable candidates would have oestrogen receptor-negative cancers, with nodal involvement and be prepared to be randomised to either chemotherapy or tamoxifen. Quality of life instruments would be required to assess endpoints other than relapse and death. Perhaps a determined clinical researcher with equally determined patients will be able to complete such a study. Until this has happened it is going to be very difficult to justify the routine use of any adjuvant chemotherapy other than tamoxifen.

1. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. *Lancet* 1992, **339**, 1–15.
2. Desch CE, Hillner BE, Smith TJ, Retchin SM. Should the elderly receive chemotherapy for node-negative breast cancer? A cost-effectiveness analysis examining total and active life-expectancy outcomes. *J Clin Oncol* 1993, **11**, 777–782.
3. Fisher B, Redmond C, Dimitrov NV, *et al.* A randomized trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node negative breast cancer who have estrogen-receptor-negative tumors. *N Engl J Med* 1989, **320**, 473–478.

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Arbiter:

S. Monfardini and F. Perrone

Direzione Scientifica, Istituto Nazionale per lo Studio e la Cura dei Tumori, Napoli, Italy

As THE article by Professor Fentiman indicates, chemotherapy cannot be considered a standard treatment for elderly women (≥ 70 years of age) with breast cancer because the number of patients who have entered clinical trials of chemotherapy is too small (less than 300) to draw any definitive conclusions, and, as pointed out by Dr Balducci and Dr Extermann, there is a trend in a reduction of efficacy of chemotherapy with increasing age [1]. However, in considering this controversial topic, it is clear that the available data on which opinions are based come from studies of postmenopausal women under the age of 70 years because no trial has yet been performed specifically in older women. Why is there no trial of this kind in the literature?

There are many reasons for this. Firstly, a number of variables could affect the design and analysis of such trials, e.g. schedule of combined chemotherapy and tamoxifen (concomitant or sequential), drug interactions in the case of concomitant administration, and oestrogen receptor (ER) expression [2]. Overall, the net benefit that one can expect from the addition of chemotherapy to tamoxifen may be very little. This is because of the trend both towards reduction in efficacy of chemotherapy with increasing age of patients and to increasing efficacy of tamoxifen with increasing numbers of ER-positive tumours, which should account for approximately 81% of cases among patients older than 65 years [3]. Toxicity—the biological and human cost of adjuvant chemotherapy—that always plays an important role in the cost/benefit balance, may be more frequent and more severe among elderly patients than among younger patients. Furthermore,

Correspondence to S. Monfardini.

the population of elderly patients is a heterogeneous mix of a minority of women with a good health and functional status and of a majority of women who have lost some function in one or more organs or systems (heart, liver, brain, lungs, kidneys, lower limbs, etc.) so that it can be difficult for them to tolerate chemotherapy.

To embark on this kind of trial would certainly not be easy (in the opinion of Professor Fentiman, it would be a Herculean task!). The required sample size would be relatively large in order to detect the small expected benefit and to account for the age-related competitive causes of mortality (a problem mentioned by Dr Balducci and Dr Extermann), which would dilute the possible benefit of chemotherapy. However, the population potentially available for this kind of trial would be very restricted, since, as Professor Fentiman reports, using chemotherapy for node-negative patients is not cost-effective [4], so one would have to select patients with adverse prognostic factors (e.g. node-positive ones or even those with more than three metastatic nodes). Also excluded would be those patients unable to consent to an experimental procedure (because of loss of cognitive functions) and those unable to comply with rules of chemotherapy (because of disability or comorbidity).

So, what should be done in future clinical research? Firstly, the avoidance of upper age limits as inclusion criteria in clinical trials of postmenopausal patients should be endorsed, with a wider use of geriatric assessment scales [5] to help physicians look for biological instead of chronological age. By doing so, more patients of advanced age but without disability, with good mental status and family support could enter clinical trials.

Secondly, for those patients who are not considered eligible for the aforementioned clinical trials because of various types of associated comorbid conditions and disabilities, there should be prospective studies on patterns of care [6]. These kinds of studies should initially be descriptive with the double aim of defining the various subsets of the population of patients (with the help of the geriatric evaluation) and the actual attitudes of physicians; the critical analysis of such studies could allow the identification of either guidelines to be proposed or unsolved controversies to be addressed in specifically designed clinical trials.

What about clinical decision-making? Taking account of characteristics of patients specifically related to old age may be helpful for clinical decision-making [7]. The application to cancer patients of multidimensional assessment tools, commonly used by geriatricians, can help in measuring the non-neoplastic comorbid conditions, disability and mental status [5] and could be a guide for physicians in the decision-making process. In this context, the addition of chemotherapy to tamoxifen should be considered when either the expected efficacy of tamoxifen is low (e.g. ER-negative tumours) or where there is strong patient motivation, with acceptance of toxicity for a possible but not huge benefit. Obviously, the evaluation of whether the patients fit the minimum requirements to tolerate chemotherapy rests with the oncologists who should use all possible tools to make the best evaluation.

Once the oncologist and the patient have decided on chemotherapy, a final point must be addressed: which chemotherapy should be preferred? In general, in younger patients, anthracycline-containing regimens seem to be considered slightly more effective than CMF schedules as adjuvant chemotherapy for breast cancer; however, more data from large clinical trials and from meta-analyses must be awaited to demonstrate definitely that this trend is true and to estimate the real net benefit possibly linked to the use of anthracyclines. Obviously, there are even less data available in the elderly. Nevertheless, the opinion of Balducci—that anthracycline-containing combinations should be preferred—might also be supported in the light of adding chemotherapy to tamoxifen, in a concomitant schedule, considering that, some years ago, a synergistic effect between these drugs was found *in vitro* by Osborne and associates in contrast with the antagonistic effect found when combining tamoxifen with melphalan [8]. Similarly, in the NSABP B-16 trial [9], a significant benefit from the addition of chemotherapy to tamoxifen was only evident when the schedule contained doxorubicin (with cyclophosphamide [AC] or with melphalan and 5-fluorouracil [PAF]) but disappeared when doxorubicin was absent (in the PF schedule). However, these data should be viewed with caution primarily because cardiac toxicity of anthracyclines might be a more serious problem in the elderly than in younger patients, particularly if combined with haematological toxicity and their possible sequelae (e.g. anaemia or febrile neutropenia), which require a good cardiac function to be tolerated by the patient. On this basis, and unless a patient has a very bad prognosis, CMF should still be considered the standard chemotherapy schedule.

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