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Current Controversies in Cancer

Should Adjuvant Chemotherapy be used to Treat Breast Cancer in Elderly Patients (≥ 70 years of age)?

L. Balducci & M. Extermann I. Fentiman S. Monfardini & F. Perrone

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L. Balducci and M. Extermann

H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, Florida 33612, U.S.A.

THE BENEFITS of adjuvant chemotherapy for breast cancer, in terms of overall survival, decrease with the age of the patients (Table 1) [1]. According to the Oxford meta-analysis, no benefits are demonstrable for women aged 70 years and over [1]. Should we, therefore, stop treating these women with adjuvant chemotherapy? Should we run randomised studies with untreated controls in this group of patients? We believe that neither solution would be wise.

Firstly, patients over 70 years of age receiving chemotherapy represented only 2% of those considered in the meta-analysis and 5% of postmenopausal women receiving chemotherapy, hardly an adequate sample from which to draw definitive conclusions. Secondly and more important, one can expect a progressive decrement in terms of overall survival with the age of the population. The incidence of comorbidity and hence of competitive causes of death increases with age [2]. For this reason, even the benefits of adjuvant treatment with tamoxifen in terms of overall survival seem to wane among the elderly [1]. Also, the prevalence of hormone receptor-rich, low proliferating tumours is higher among the elderly [3]. These tumours may assume a more indolent course and never become life-threatening during a woman's lifetime. However, despite these considerations, breast cancer is still a lethal and highly debilitating disease for older women and prevention of recurrence may improve both the survival and the quality of life of older women with early breast cancer.

We will try to frame this discussion within three questions: Is treatment effective? Which treatment is effective? Who should be treated?

As far as we know, there is no reason to set apart the effectiveness of adjuvant chemotherapy among older women from the wider issue of adjuvant chemotherapy in postmenopausal women. There are at least seven clinical trials that attest to the ability of adjuvant chemotherapy to improve the overall survival of postmenopausal women with breast cancer (Table 2) [4–10], and many more trials demonstrate a prolongation of disease-free survival from adjuvant chemotherapy [11–13]. All these trials included women with involved axillary lymph node or women with negative axillary lymph node who had receptor-poor tumours ≥ 1 cm in diameter and in the following discussion we will refer to these women. Women with hormone receptor-rich tumours and, in some studies, also those with hormone receptor-poor tumours were concomitantly treated with tamoxifen for 2–5 years. In many trials, control subjects received tamoxifen and were compared with patients receiving chemotherapy and tamoxifen.

We know of no biological reason why the benefits of adjuvant chemotherapy should not extend to women aged 70 years and older, as long as they can tolerate the treatment and their life expectancy is not curtailed by other diseases. Thus, effectiveness of treatment by itself is not an issue.

More complex is the question related to optimal treatment. In this context, it is important to separate patients by nodal status and hormone receptor status. For hormone receptor-negative, lymph node-negative patients, a CMF (cyclophosphamide, methotrexate, 5-fluorouracil) type combination appears active (Table 2). For patients whose tumour is hormone receptor-positive and involves the axillary lymph nodes, only anthracycline-containing combinations of chemotherapy have consistently improved overall survival. The most noticeable exception to this rule has been the Italian study from the GROCTA group, which showed a shortening of patient's survival with the addition of a combination of agents including epirubicin to tamoxifen [14]. However, the schedule of administration (poorest drug first) might have jeopardised the results of the study. However, none of the studies using CMF-like combinations of chemotherapy in combination with tamoxifen, such as the SWOG [15], the ECOG [16] and the Canadian studies [17], as well as the Ludwig

Correspondence to L. Balducci.

Table 1. Reduction in recurrence rate and mortality by adjuvant chemotherapy in postmenopausal women with breast cancer [1]

Age group	Number of patients	Recurrence rate	Mortality
50–59	3128	29% ± 5	13% ± 7
60–69	3874	20% ± 5	10% ± 6
70 +	274	—	—

III study [8], could demonstrate any survival benefit of chemotherapy when compared with tamoxifen alone in these patients.

For patients with hormone receptor-poor tumours that involve the axillary lymph nodes, the situation is even more confusing. The SWOG study comparing CMFVP (CMF, vincristine, prednisone) with melphalan showed the superiority of combination chemotherapy over single-agent chemotherapy, while the NSABP-B11 and B12 [6] studies, comparing melphalan–5-fluorouracil with melphalan–5-fluorouracil and doxorubicin, showed the superiority of the anthracycline-containing chemotherapy. The Ludwig study, using CMFP (CMF, prednisone), showed a modest improvement in survival in women with hormone receptor-poor tumours [8].

In our opinion, anthracycline-containing combination chemotherapy is the only one which has produced consistent results in postmenopausal women and should be preferred if contra-indications to treatment are not present. Of interest, the NSABP B-15 compared CMF for six courses and CA (cyclophosphamide, doxorubicin) for four courses and found CA to be better tolerated [18]. This study made the issue of CMF versus anthracycline all but moot for older individuals.

The third question—who should be treated—should be answered by judgement and experience and is the one which should most attract future research. The issues are life expectancy, risk of recurrence, quality of life and risk of treatment-related complications. As an optimal effect of adjuvant treatment takes 2 years to achieve and median survival after relapse is 2 years, any woman with a life expectancy in excess of 2 years should be treated, if treatment is indicated. Life expectancy is a function of age, comorbidity and functional status and may be computed from these parameters [19]. The risk of recurrence may be estimated from the number of involved lymph nodes, and in patients with uninvolved lymph nodes, from the tumour size, the concentration of hormone receptors, the grade and the proliferative index of the tumour.

However, even when this information is available, one variable is provider-independent and requires direct participation of the patient and that is the balance between risk of tumour recurrence and risk of treatment complications acceptable to individual patients. Quality of life studies may suggest which course of action may be preferable to the majority of patients [21] and this information should be made available to individual patients to assist them in their decisions.

A number of questions related to adjuvant chemotherapy in older individuals are still unanswered. These include the effects of cancer and chemotherapy on the quality of life of older individuals; the effectiveness of new drugs, such as mitoxantrone, navelbine, paclitaxel or docetaxel which may be better tolerated by older individuals; the addition of cardioprotectors, such as desrazoxane, in anthracycline-containing combinations of chemotherapy and the use of liposomal doxorubicin; the value of chemotherapy in addition to tamoxifen in patients with hormone receptor-rich tumours and uninvolved lymph nodes, at increased risk of relapse from large tumour size, poor histological differentiation or high proliferation rate; and the addition of tamoxifen to chemotherapy in hormone receptor-poor tumours. The most recent update of the Oxford meta-analysis suggests that this addition may be beneficial, probably due to the fact that tamoxifen may reverse multidrug resistance [20].

In our opinion, a group of untreated control patients is no longer acceptable. Controls with hormone receptor-rich tumours and uninvolved lymph nodes should receive tamoxifen. All other patients with tumours ≥ 1 cm in diameter should receive chemotherapy and preferentially an anthracycline-containing combination of chemotherapy.

Table 2. Randomised clinical trials of adjuvant chemotherapy in postmenopausal women positive for both disease-free and overall survival

Study	No. of patients	Upper age (years)	Characteristics	Regimen	Outcome difference* DFS	Outcome difference* OS
NSABP-B13 [4]	280	60	LN–; ER–	M–F versus O	17%	14%
Intergroup [5]	159	70	LN–	CMFp versus O	19%	15%
NSABP-B11 [6]	281	59	LN+; PR–	PAF versus PF	7%	6%
NSABP-B16 [7]	1245	70	LN+; PR+‡	ACT versus T	17%	10%
Ludwig III [8]	463	65	LN+; HR+/HR–	CMFpT versus pT versus O	21% versus 0 10% versus pT	16% versus 0 12% versus pT†
ICCG [9]	604	75	LN+; HR+	ET versus T	27%	9%
SWOG [10]	214	NS	LN+	CMFVp versus p	14%	12%

NSABP, National Surgical Adjuvant Breast and Bowel Project; ICCG, International Collaborative Cancer Group; SWOG, Southwest Oncology Group. ER, Oestrogen receptor; HR, hormone receptor; PR, progesterone receptor; LN, lymph nodes; A, doxorubicin (adriamycin); C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; M, methotrexate; O, observation; P, phenylalanine mustard (melphalan); p, prednisone; T, tamoxifen; V, vincristine. M–F, sequential methotrexate and fluorouracil.

*At time of cited publications, in favour of the first arm. †Survival advantage limited to women with hormone receptor-poor tumours. ‡Patients over 60 years might have had PR poor tumours; according to the NSABP definition, all tumours in women over 60 years were considered responsive to tamoxifen.

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Contra:

I.S. Fentiman

ICRF Clinical Oncology Unit, Guy's Hospital, London SE1 9RT, U.K.

ALTHOUGH THERE may be an adjuvant benefit for patients with colorectal cancer who are given 5-fluorouracil, breast cancer is the only solid tumour in which adjuvant therapy has been confirmed as effective. The second meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has led to a change of attitude towards adjuvant therapy in older women [1]. The overview shows clearly that the magnitude of the effect of tamoxifen is equally large in postmenopausal women of all age groups and indeed that there may be a slightly larger mortality reduction in women aged over 70 years, as summarised in Table 1.

Additionally, the meta-analysis shows that there is a significant but smaller effect of chemotherapy in women aged 50–69 years. It is not possible to give an accurate estimate of the effect in those over 70 years of age because of the small numbers in this age group randomised within controlled trials. The likelihood of benefit for all subgroups with breast cancer has meant that the more hawkish medical oncologists have argued that older women should be given adjuvant chemotherapy, particularly those with oestrogen receptor-negative cancers.

To address this problem, Desch and associates created a Markov model to assess the survival benefit and cost-effectiveness of adjuvant chemotherapy in older women with node-negative breast cancer [2]. Recurrence rates were based upon the EBCTCG meta-analysis, together with likelihood of recurrence in node-negative cases using data from the NSABP B13 study [3]. Chemotherapy was assumed to comprise cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Other assumptions were that chemotherapy would