Progress in the treatment of breast cancer in the elderly

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Introduction

More than one third of all breast cancers occur in women >70 years of age, but adequate directives for their treatment are often lacking, because these patients have often been excluded from clinical trials. Although justified by many questionable reasons, such an exclusion is difficult to understand, as a 70 year old woman has a median life expectancy of 15.5 years, i.e. half of them will live much longer. Older and younger women with operable breast cancer have a similar prognosis but older women are more likely to have metastatic disease at diagnosis, and to die from intercurrent disease [1].

The largest series reporting on biological differences in breast cancer among patients of various age groups originally reported on 9228 patients, of whom 2919 were ≥65 years of age. The investigators showed that elderly women have a higher frequency of hormone receptor positive tumors [84% estrogen receptor (ER) positive versus 67% in younger patients], and 58% (compared with 50%) are diagnosed with node negative disease although 20% had tumors >5 cm, versus 13% of those <65 years of age [2].

Co-morbidity: a complicating issue

A likely reason for non-participation in clinical trials is the number of co-existing illnesses which increases with advancing age. Thus, the percentage of women with breast cancer who actually die of breast cancer decreases with age [3]. Several well defined and validated scales for measuring co-morbidity (Charlson, CIRS-G) have been shown to correlate with outcomes such as mortality, hospitalization duration or disability in various populations outside geriatric oncology [4]. The Charlson scale focuses on a short list of selected diseases and is aimed at simplicity. It is based on the 1 year mortality of patients admitted to a medical hospital service. The CIRS-G is aimed at comprehensiveness and allows rating of all diseases encountered. The CIRS-G has a structure analogous to the World Health Organization (WHO) or National Cancer Institute (NCI) toxicity scales, well known to medical and radiation oncologists. This scale classifies co-morbidities into 14 organ systems and grades each condition from 0 (no problem) to 4 (severely incapacitating or life-threatening condition). Scores may be summarized in different ways, with comparable results. The scale encompasses both potentially lethal and non-lethal co-morbid conditions. Similar scales are combined along various other instruments for evaluation of the elderly into a comprehensive geriatric assessment (CGA). It has recently been proven that the CGA adds information with respect to the Eastern Cooperative Oncology Group performance status (PS). The investigators studied 363 elderly cancer patients (195 males, 168 females; median age, 72 years) with solid (n = 271) or hematological (n = 92) tumors. In addition to PS, their physical function was assessed by means of the activity of daily living (ADL) and instrumental activities of daily living (IADL) scales. Co-morbidities were categorized according to Satariano’s index. By multivariate analysis, elderly cancer patients who were ADL-dependent or IADL-dependent had a nearly two-fold higher probability of having an elevated Satariano’s index than independent patients. A strong association emerged between PS and CGA, with a nearly five-fold increased probability of having a poor PS (i.e. ≥2) recorded in patients dependent for ADL or IADL [5].

Localized disease

Primary medical treatment

Uncontrolled studies published in the early 1980s suggested that tamoxifen as sole treatment was effective in elderly patients with breast cancer. Randomized trials show similar results but make different conclusions. In each of these trials elderly women with primary breast cancer were randomized to receive either tamoxifen versus primary breast cancer surgery or tamoxifen versus primary surgery followed by tamoxifen. One study concluded that surgery should be reserved for tamoxifen failure [6]. Robertson et al. [7] showed that following surgery plus tamoxifen, 70% of women were free of local disease while following tamoxifen alone, only 47% were. A randomized study for the Elderly Breast Cancer Working Party showed that quality of life and survival were not different between tamoxifen alone and surgery alone but that more women in the tamoxifen alone arm required a change in management, often because of local or locoregional progression [8]. However, the conclusion has come from a joint analysis of Italian and UK data, which shows that breast cancer specific survival is worse in women treated with tamoxifen alone [9]. More modern studies, which also take into account hormone receptor positivity, have indicated that
antiaromataxes, letrozole, anastrozole and exemestane are highly effective in this setting [10, 11]. The most important trial to date in this field is a randomized, double-blind, multicenter study which was conducted to compare the anti-tumor activity of letrozole 2.5 mg versus tamoxifen 20 mg in 337 postmenopausal women with ER and/or progesterone receptor (PgR) positive primary untreated breast cancer [12]. At baseline none of the patients were considered to be candidates for breast-conserving surgery (BCS) and 14% of the patients were considered inoperable. The primary endpoint was to compare overall objective response [(complete response (CR) + partial response (PR)) determined by clinical palpation. Overall objective response rate (clinical palpation) was statistically significantly superior in the letrozole group (55%) compared with tamoxifen (36%) (P < 0.001). Secondary endpoints of ultrasound response, 35% versus 25% (P = 0.042); mammographic response, 34% versus 16% (P < 0.001) and BCS, 45% versus 35% (P = 0.022) between the letrozole and tamoxifen groups, respectively, showed letrozole to be significantly superior. It is important to note that data suggest that patients who do not respond to endocrine treatments within the first 3 months are unlikely to gain any significant reduction in volume by continuing with treatment for a longer period before surgery (M. Dixon, personal communication).

Surgery
Advanced age per se is a risk factor for surgical undertreatment, even if older women tolerate breast surgery well [13]. Operative mortality rates of between 1% and 2% have however been reported [14, 15]. The main factor influencing surgical morbidity and mortality is not age but the presence of co-existent disease. Progress in anesthesiology should allow appropriate procedures for almost any woman requiring breast surgery [16].

Radiation therapy
The Milan III randomized trial was a randomized study comparing quadrantectomy axillary dissection and radiotherapy (QUART) and quadrantectomy and axillary dissection without radiotherapy (QUAD) [17]. From 1987 to 1989, 579 women with carcinoma of the breast <2.5 cm in maximum diameter were randomly assigned to quadrantectomy, axillary dissection and radiotherapy (n = 299) and to quadrantectomy with axillary dissection without radiotherapy (n = 280). Primary end points were intra-breast tumor reappearance (IBTR) and all-cause mortality. The number of IBTRs was significantly higher in patients treated with surgery alone (59 of 273; 10-year crude cumulative incidence of 23.5%) than in patients treated with surgery plus radiotherapy (16 of 294; 10-year crude cumulative incidence of 5.8%). The difference in IBTR frequency between the two treatments appeared to be particularly high in women <45 years of age, tending to decrease with increasing age up to no apparent difference in women >65 years of age. Overall survival curves for the two groups did not differ significantly (P = 0.326). However, a limited survival advantage was evident after radiotherapy for node-positive women. The authors conclude that these data suggest that radiotherapy may be avoided in patients >65 years of age, and may be optional in women aged 56–65 years with negative nodes. These data are in contradiction with other series that show no such ‘age-related protection from local relapse’ [18]. However, a study specifically designed to address this issue has been reported in preliminary form. The Cancer and Leukaemia Group B (CALGB), Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG) joined forces to compare lumpectomy plus tamoxifen (T) with and without radiotherapy (RT) in women ≥70 years of age with clinical stage I, ER+ breast carcinoma. From July 1994 to February 1999, 647 women entered the study. With a median time on study of 28 months, the rate of locoregional failure was extremely low. Six out of 319 women developed locoregional recurrences (four breast, two axilla) on T [annual rate = 0.9%] versus 0/317 on T+RT (P = NS). Four out of 319 women developed contralateral breast cancer on T versus 5/317 on T+RT. Physicians and patients considered breast appearance and texture worse on T+RT. The authors conclude that RT, when added to tamoxifen, led to fewer locoregional recurrences (P = NS). At this period of follow-up, the addition of RT has no impact on ultimate breast conservation, survival, disease-free survival and breast cancer specific mortality. Despite the relatively short follow-up, the high incidence of death from other causes, the low rate of in breast recurrence (similar to contralateral breast cancer rate) and the feasibility of breast preservation after in-breast recurrence raises the possibility that RT may not have clinical benefit in this population [19].

Adjuvant therapy
The Oxford Overview has shown the benefits of adjuvant tamoxifen therapy in women aged 70 years, the recommended standard in elderly patients with estrogen receptor positive tumors. The proportional reduction in breast cancer relapse and mortality are similar for women with node-negative and node-positive disease while chemotherapy has not been evaluated in sufficient numbers of women >65 years of age [20, 21]. Anastrozole, tamoxifen, alone or in combination (ATAC), evaluating 9366 postmenopausal breast cancer patients in 21 countries, was presented at the San Antonio Breast Cancer Symposium in December 2001. The trial compared three treatment groups. One group used the current standard treatment tamoxifen, a second used anastrozole and a third used a combination of the two. Women who were given anastrozole showed a 17% reduction in risk of disease recurrence compared with women who were given tamoxifen. After a median of 33 months follow-up and a median duration of treatment of 30.7 months, anastrozole monotherapy was found to be significantly more effective in prolonging disease-free survival (DFS) than tamoxifen. Only 317 of 3125 women in the
anastrozole group had a relapse of their breast cancer or died
compared with 379 of 3116 women in the tamoxifen group
\( P = 0.0129; \) hazard ration (HR) = 0.83; confidence interval
(CI) 0.71–0.96). The study had some problems, and the
investigators are doing their best to confirm the hormone-
receptor status of most patients. Among women with con-
firmed hormone-sensitive tumors, the reduction in risk with
anastrozole compared with tamoxifen was, as expected, even
more striking at 22% \(( P = 0.0054; \) HR = 0.78; CI 0.65–0.93).
Anastrozole use was also associated with fewer side effects
than tamoxifen, notably (as hoped for) less uterine cancer, but
unfortunately with more ‘skeletal events’. This latter issue
mandates caution in the premature use of anastrozole as an
adjuvant treatment in elderly patients at risk for osteoporosis
[22].

Tamoxifen remains currently the ‘gold standard’ for adjuv-
ant breast cancer treatment for all women with estrogen/pro-
gesterone receptor positive breast cancer. However, emerging
data indicate that women whose tumor co-expresses too
many HER-2 receptors might have an advantage if they used
an anti-aromatase, as tamoxifen is less effective in such cases
[23]. Many other determinants of outcome exist, and the
emergence of micro-array analyses will revolutionize our
approach to all cancers, along with the development of drugs
which will be more and more specifically active on single
mechanisms [24].

In the adjuvant chemotherapy trials considering the meta-
analysis, only 600 women were included ≥70 years of age and
the sample size was insufficient to determine the benefits of
chemotherapy in this age group [20]. However, the propor-
tional benefits of chemotherapy in patients >70 years of age
are unlikely to be significantly different from postmenopausal
women from 50 to 60 years of age and for these women the
proportional risk reductions following chemotherapy were
20% (SD 3) for recurrence and 11% (SD 3) for overall mortal-
ity. The updated ‘2000’ overview data have been stated to
confirm these data. The issue of adjuvant chemotherapy in the
elderly is a subject of controversy, and only one specific study
has been designed recently in the USA, which was finally
accepted by the ethical committees after much debate. Node-
positive, ER negative elderly patients will be randomized to
doxorubicin-cyclophosphamide (AC), cyclophosphamide-
lethamide-5-fluorouracil (CMF) or oral capecitabine. The
lack of a control no chemotherapy arm is quite remarkable.
Other alternatives are discussed by groups such as Breast
Cancer International Research Group (BCIRG), European
Organisation for Research and Treatment of Cancer (EORTC)
and International Breast Cancer Study Group (IBCSG).

A presentation at ASCO 2002 justifies the efforts in evalu-
ating chemotherapy in breast cancer patients >65 years of age.
A French cooperative group has reported on a disease-free
survival (DFS) advantage of weekly epirubicin plus tamoxifen
versus tamoxifen (Tam) alone as adjuvant treatment of oper-
able, node-positive elderly breast cancer patient after 5-years
of follow-up (FASG-08 trial). The aim of the relatively small
study was to evaluate the contribution of epirubicin as adjuvant treatment of N+ elderly breast cancer patients in
terms of DFS. Between 1991 and 2001, 338 patients >65 years
of age with operable breast cancer were randomized after
surgery. Among these patients, 13% had negative hormone
receptors. Arm A (Tam, \( n = 164 \)), tamoxifen 30 mg/day for
3 years; arm B (E-Tam, \( n = 174 \)), epirubicin 30 mg × 3 (days 1,
8 and 15) every 28 days for six cycles plus tamoxifen 30 mg/day
for 3 years. In both arms, locoregional radiotherapy was
delivered, after chemotherapy in arm A. At the median follow-
up of 64 months 26.5% relapses were seen on Tam versus
22.1% with E-Tam: the relative risk (RR) of relapse was 1.85
(1.59–2.11) with Tam alone (\( P = 0.02 \)) and median time to
relapse was 19 and 33 months, respectively (\( P = 0.07 \)). Deaths
related to disease progression were infrequent with 19.1% and
17.2% deaths, respectively (\( P = 0.67 \)) [25].

Treatment of metastatic disease

Endocrine therapy is the standard primary and most often
second- or even third-line treatment for women with hormone
receptor positive metastatic disease. In elderly patients with
hormone receptor negative metastatic breast cancer whose
disease is not rapidly progressive or life threatening, endo-
crine therapy should be considered if there is uncertainty
about the determination of receptor positivity or if the clinical
behavior of the tumor suggests possible endocrine responsive
disease. Pivotal studies [26, 27] have shown that letrozole and
anastrozole have an advantage over tamoxifen in the meta-
static setting, and early presentations of exemestane data
suggest similar results.

Chemotherapy in the metastatic setting needs careful
consideration of the patient’s co-morbid status to adapt doses
[3]. More recent guidelines are not available, and specific drug
related guidelines for elderly patients have only emerged for
capcitabine, which should have a dose adaptation in relation to
creatinin clearance (see product label), a common issue in the
elderly.

Bisphosphonates are recommended for all patients with
lytic bone metastases. The choice between the various intra-
venous forms is still a matter of debate.

Conclusion

Progress in the treatment of breast cancer in the elderly, who
have several co-morbidities, is slow in coming. However, data
are emerging for a subset of fit patients to justify the evalu-
ation of adjuvant chemotherapy and decreasing the use of
adjuvant radiation therapy. More data on the long-term
tolerance of antiaromatases is needed in elderly patients, es-
specially with respect to adverse skeletal events.
References


