Any Progress in 2006 in Breast Cancer in the Elderly?

a report by
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In North America and Europe, half to one-third of all breast cancers occur in women over 65. Yet these patients are excluded from clinical trials, and, therefore, adequate directives for their treatment are often lacking. Although justified by many bad reasons, such an exclusion is difficult to understand, as women aged 70 have 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.

The first large series reporting on biological differences in breast cancer among patients of various age groups originally reported on 9,228 patients, of whom 2,919 were aged 65 and over. The investigators showed that older women have a higher frequency of hormone receptor-positive tumours (84% oestrogen receptor (ER)-positive versus 67% in younger patients), and 58% (compared with 50%) are diagnosed with node-negative disease, although 20% had tumours above 5cm, versus 13% of those below the age of 65. Another large series comes from the National Cancer Institute (NCI) in Milan, with 1,289 patients above the age of 75 in a cohort of 14,007 patients. This series from the Italian NCI, along with results from two other recent series, do not confirm the initial data about node-negativity being more frequent in spite of a larger tumour size.

Molino and colleagues evaluated a group of 3,814 patients with invasive, operable breast cancer divided into five groups based on their age at diagnosis. Univariate analysis showed that the elderly women had larger tumours with more axillary node involvement and lymphovascular invasion, more ER and progesterone receptor (PR)-positive tumours, lower grades and proliferative indices, and were less likely to be c-erbB2, positive. Similar results have been identified in a group of post-menopausal patients above 75 years of age, who constituted 146 of the 2,999 patients evaluated in a cohort of the European Institute of Oncology (EIO) study. These patients referred to surgery had larger tumours compared with younger post-menopausal patients (pT4: 6.7% versus 2.4%), as well as greater lymph node involvement (lymph node positive: 62.5% versus 51.3%).

Screening

Many countries have an upper age limit of 70 years for screening for breast cancer, though there are data showing that the limit should be at least 75 years. However, above this age, most tumours might be biologically less aggressive and possibly the confounding factors of increased co-morbidity could detract from the benefits of early detection. As prospective screening studies are unlikely to be performed in this age group, authorities will have to look at some pragmatic rules that take the general physical status of the person into account to decide if, from a national health perspective, screening above the age of 75 can be justified in all or only some people.

Comorbidity – A Complicating Issue

A likely reason for non-participation in screening programmes and clinical trials is the number of co-existing illnesses that increase with advancing age. Thus, the percentage of women with breast cancer who actually die of the disease decreases with age. Several well-defined and validated scales for measuring comorbidity (Charlson, and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)) have been shown to correlate with outcomes such as mortality, hospitalisation duration or disability in various populations outside geriatric oncology.

The Charlson scale focuses on a short list of selected diseases and is aimed at simplicity. It is based on the one-year mortality of patients admitted to a medical hospital service. The CIRS-G, on the other hand, 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 the 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). Scores may be

summarised in different ways, with comparable results. The scale encompasses both potentially lethal and non-lethal comorbid conditions.

Similar scales are combined along various other instruments for evaluation of the elderly into a Comprehensive Geriatric Assessment (CGA). It has been proven that the CGA adds information with respect to the Eastern Cooperative Oncology Group (ECOG) performance status. The investigators studied 363 elderly cancer patients (195 males, 168 females; median age, 72 years) with solid (n=271) or haematologic (n=92) tumours. In addition to performance status (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 categorised 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. > or =2) recorded in patients dependent for ADL or IADL. However, the use of these approaches is still limited to specialised centres, and there is a need for simplification of these assessments. The International Society of Geriatric Oncology (SIOG) has therefore created a task force to review the evidence on the use of a CGA in cancer patients. Several biological and clinical correlates of ageing have been identified, and these include albumin level, calculated creatinine clearance and possibly haemoglobin. Their relative weight and clinical usefulness is still poorly defined. There is strong evidence that a CGA detects many problems missed by a regular assessment in general geriatric and in cancer patients, and that it improves function and reduces hospitalisation in the elderly. There is also heterogeneous evidence that a CGA improves survival and is cost-effective. There is corroborative evidence from a few studies conducted in cancer patients. Screening tools exist and have been successfully used in settings such as the emergency room, but globally they are poorly tested. The task force could not recommend any specific tool or approach above others.

Localised Disease – Primary Medical Treatment

Uncontrolled studies published in the early 1980s suggested that tamoxifen as the sole treatment was effective in elderly patients with breast cancer. Randomised trials show similar results but reach different conclusions. In each of these trials, elderly women with primary breast cancer were randomised 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. Robertson and his colleagues showed that following surgery plus tamoxifen, 70% of women were free of local disease while following tamoxifen alone, only 47% were. A randomised 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. 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. More modern studies, which also take into account hormone receptor positivity, have indicated that aromatase inhibitors letrozole, anastrozole and exemestane are highly effective in this setting.

The most important trial to date in this field is a randomised, double-blind, multicentre study which was conducted to compare the anti-tumour activity of letrozole 2.5mg versus tamoxifen 20mg in 337 post-menopausal women with oestrogen receptor (ER) and/or PgR-positive primary untreated breast cancer. 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 end-point 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 end-points of ultrasound response, 35% vs 25% ($p=0.042$), mammographic response, 34% vs 16% ($p<0.001$), and BCS, 45% vs 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 three months are unlikely to gain any significant reduction in volume by continuing with treatment for a longer period before surgery.

A Cochrane analysis has reviewed the evidence from randomised trials comparing primary endocrine therapy with tamoxifen (endocrine therapy alone) to surgery, with or without adjuvant endocrine therapy, in the management of women aged 70 or over with operable breast cancer. Hazard ratios (HR) were derived for time-to-event outcomes where possible, and a fixed-effect model was used for meta-analysis. Seven eligible trials were identified of which six had published time-to-event data and one was published

only in abstract form with no useable data. The quality of the allocation concealment was adequate in three studies and unclear in the remainder. In each case, the endocrine therapy used was tamoxifen. Looking at data based on an estimated 869 deaths in 1,571 women, these researchers were unable to show a statistically significant difference in favour of either surgery or primary endocrine therapy in respect of overall survival. However, there was a statistically significant difference in terms of progression-free survival (PFS), which favoured surgery with or without endocrine therapy. The HR for overall survival were: 0.98 (95% confidence interval (CI) 0.74–1.30, p=0.9) for surgery alone versus primary endocrine therapy; 0.86 (95% CI 0.73–1.00, p=0.06) for surgery plus endocrine therapy versus primary endocrine therapy. The HRs for PFS were: 0.55 (95% CI 0.39–0.77, p=0.0006) for surgery alone versus primary endocrine therapy; 0.65 (95% CI 0.53–0.81, p=0.0001) for surgery plus endocrine therapy versus primary endocrine therapy (each comparison based on only one trial). They concluded that primary endocrine therapy should only be offered to women with ER-positive tumours who are unfit for or who refuse surgery, but stated that in a cohort of women with significant co-morbid disease and ER-positive tumours it is possible that primary endocrine therapy may be a superior option to surgery.

Surgery

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

Radiation Therapy

The Milan III randomised trial compared quadrantectomy axillary dissection and radiotherapy (QUART) and quadrantectomy and axillary dissection without radiotherapy (QUAD). Between 1987 and 1989, 579 women with carcinoma of the breast less than 2.5cm in diameter were randomly assigned to QUART (299) and to QUAD (280). Primary end-points were intra-breast tumour reappearance (IBTR) and all-cause mortality. The number of IBTRs was significantly higher in patients treated with surgery alone (59 cases out of 273; 10-year crude cumulative incidence of 23.5%) than in patients treated with surgery plus radiotherapy (16 cases out 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 up to 45 years of age, tending to decrease with increasing age up to no apparent difference in women older than 65 years. Overall survival (OS) 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 concluded that these data suggest that radiotherapy may be avoided in patients older than 65, 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", even if a recent study suggested a similar conclusion.

The Cancer and Leukemia Group B (CALGB), Radiation Therapy Oncology Group (RTOG) and ECOG joined forces to compare lumpectomy plus tamoxifen (T) with and without radiotherapy (RT) in women 70 years of age or older with clinical stage I, ER-positive 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%] vs 0/317 on T+RT (P=NS). Four out of 319 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 concluded 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, DFS 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.

A recent report of a study evaluating the effect of RT omission on survival in older breast cancer patients treated with BCS highlights the fact that some of the studies that suggested no impact on survival but only an increased risk of local failure might have had a too short a follow-up. A total of 4,836 women aged 50 to 89 with T1-T2, N0-N1, M0 breast cancer were evaluated. Tumour and treatment factors, relapse rates and OS and breast cancer-specific survival (BCSS) were compared between women treated with and without RT in three age categories: 50 to 64 (n=2398), 65 to 74 (n=1665), and >/=75 years (n=773). This study had a median follow-up of 7.5 years. Rates of RT

omission significantly increased with advancing age (7%, 9%, and 26% in age 50–64, 65–74, and >/=75 years respectively, p<.0001). RT omission was associated with significantly reduced local control, BCSS, and OS and this despite similar tumour characteristics and higher rates of systemic therapy use in women aged >/=75 years. As stated by the authors, these findings support the hypothesis that inadequate local therapy is associated with reduced survival in elderly women treated with BCS.

Another group has similarly attracted our attention to the importance of local control. This group of investigators used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database from 1 January 1992, through 31 December 31 1999, to identify 8,724 women aged 70 years or older treated with conservative surgery for small, lymph node-negative, ER-positive (or unknown receptor status) breast cancer. They used a proportional hazards model to test whether radiation therapy was associated with a lower risk of second ipsilateral breast cancer or subsequent mastectomy reported by Medicare claims. Radiation therapy was associated with an absolute risk reduction of 4.0 events per 100 women at five years (i.e. from 5.1 events without radiation therapy to 1.1 with radiation therapy) and 5.7 events per 100 persons at eight years (i.e. from 8.0 events without radiation therapy to 2.3 with radiation therapy) (p<.001, log-rank test). Importantly these authors looked at the influence of co-morbidity and showed that radiation therapy was most likely to benefit those aged 70–79 years without co-morbidity (number needed to treat (NNT) to prevent one event = 21 to 22 patients) and was least likely to benefit those aged 80 years or older with moderate to severe co-morbidity (NNT=61 to 125 patients).

It should be remembered that while one awaits long-term results of the very promising peri-operative radiation techniques, which should spare several weeks of travel for treatment, there are also, among the elderly, patients who cannot undergo surgery. Surgery has been shown in several studies to be a factor for long-term disease control and survival, but there can still be inoperable patients. These rare patients might benefit from shorter courses of radiation, as described in a report on 115 patients with a median age of 83 presenting with 124 non-metastatic breast carcinoma who were treated with definitive once weekly hypofractionated radio-therapy associated with hormonal therapy. Radiation was delivered as once-a-week, 6.5Gy for a total breast dose of 32.5Gy in five fractions, followed with 1–3 fractions of 6.5Gy to the tumour site. The median follow-up is short at 41 months and the five-year local progression-free rate was 78%.

Adjuvant Therapy

The Oxford Overview has shown the benefits of adjuvant tamoxifen therapy in women aged 70 years, the discussed standard in elderly patients with ER-positive tumours. 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 above age 70. Trials with aromatase inhibitors have not yet convinced that these should always replace tamoxifen in the adjuvant setting, and certainly in the elderly one wants to know if the increased number of 'skeletal events' observed in younger post-menopausal patients is also a clinically relevant issue. At least in younger patients, the efficacy of zoledronic acid – a potent intravenous bisphosphonate – in reducing the number of such events is very promising. The St Gallen consensus does not have specific recommendations for patients above a certain age limit.

In the adjuvant chemotherapy trials considered in the meta-analysis, the number of women included over 70 years or older was insufficient to confidently determine the benefits of chemotherapy in this age group. However, the benefits of chemotherapy in patients aged over 70 are unlikely to be significantly different from post-menopausal women from 50 to 69 years old. The overview data published in 2005 indicate that for these women the absolute mortality reduction following chemotherapy versus control in ER-negative node-positive patients is 9.6% (mortality decreases from 42.9% to 33.3%) at five years and 4.9% (decreases from 28.9% to 24%) in ER-positive patients when comparing chemotherapy and tamoxifen with tamoxifen alone. The issue of adjuvant chemotherapy in the elderly remains the subject of controversy, and several studies are on-going. In the US, node-positive ER-negative elderly patients are randomised to AC (doxorubicin/cyclophosphamide), CMF (cyclo-phosphamide/methotrexate/5-fluorouracil) or oral capecitabine.

The lack of a control no-chemotherapy arm is quite remarkable, indicating that the investigators believe that chemotherapy indeed has no artifical age-limit to be active when the tumour biology shows that it is probably needed. The German Breast Group (GBG) has started a study evaluating the role of bisphosphonates in elderly patients with ER-negative tumour receiving either no chemotherapy or capecitabine. The International Breast Cancer Study Group (IBCSG) has decided to evaluate pegylated liposomal doxorubicin versus nil or versus (center and patient decision) metronomic chemotherapy with low-dose cyclophosphamide and methotrexate. Both groups have agreed on a

similar evaluation of the elderly patients to validate the predictive value of the Charlson score, the Vulnerable Elders Survey (VES)-13 analysis, haemoglobin and albumin levels, and calculated creatinine clearance.

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, endocrine therapy should be considered if there is uncertainty about the determination of receptor positivity or if the clinical behaviour of the tumour suggest a possible endocrine responsive disease. Pivotal studies have shown that anti-aromatases have an advantage over tamoxifen in the metastatic setting.

Chemotherapy in the metastatic setting needs careful consideration of patients' co-morbid status to adapt doses. Recently, the clinical value of complex regimens has been called into question as several drugs used alone (monotherapy) or in sequence (serial single agent) have been shown to be both efficacious and better tolerated The International Society of Geriatric Oncology (SIOG) is working on specific guidelines and some indications are already available. Specific drug-related guidelines for elderly patients have emerged for capecitabine, which should have a dose adaptation in relation to creatinine clearance (see product label), a common issue in the elderly. A recent review indicates its safety and efficacy also in elderly patients. Another emerging agent is pegylated liposomal doxorubicin, which has no cardiac toxicity issue and seems to be safe and well tolerated at a dose of 50mg/m^2 every four weeks in fit elderly. Oral vinorelbine and gemcitabine are other agents of interest in the elderly breast cancer patients. Bisphosphonates are recommended for all patients with lytic bone metastases. The choice between the various intravenous and oral forms is still a matter of debate.

Conclusion

Progress in screening and treatment of breast cancer in the very elderly who have several comorbidities is not readily available. Surgery remains a key factor in early disease. Fit patients should be evaluated for adjuvant chemotherapy, if possible within on-going studies, and the use of adjuvant radiation therapy remains a priority in patients operated conservatively. More data on the long-term tolerance of anti-aromatases is needed in elderly patients, especially because of concern for skeletal events. In the metastatic setting, oncologists are learning how best to use available agents, using appropriate supportive therapy when needed. Finally, it is worth noting that this article did not address the tolerability of newer biological agents in the elderly. ■

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