NEW ASPECTS IN THE TREATMENT OF GYNECOLOGICAL CANCERS

Edited by
J. Sehouli and W. Lichtenegger

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J. Sehouli, E. Özcelik, D. Könsgen, A. Mustea

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Abstract. Due to improved life expectancy and the increase in incidence of breast cancer in old age, ever more older women are developing this disease. Although there is only limited evidence-based data from randomized trials on the treatment, older patients are still under-represented in clinical studies, and currently there is no clear consensus on chemotherapy treatment for older women with breast cancer. Adjuvant therapy strategies, in particular, suffer from a lack of uniform standards and reflect a generally less aggressive treatment. Recently published studies have shown that older women suffering from breast cancer can also profit from a treatment based on therapeutic standards and consensus guidelines. In spite of developments in adjuvant chemotherapy using increased amounts of therapeutic agent to improve survival, many older patients receive instead reduced quantities of chemotherapeutic agent. Thus, the questions arise, whether undertreatment of older patients with breast cancer can lead to a poorer outcome or whether new therapy strategies, for example dose-intensive chemotherapy, can be used with older patients.

Is undertreatment a prognostic factor?

One aspect of adjuvant chemotherapy that has emerged as a predictor of outcome is whether patients receive the full, prescribed dose. In a 20-year study of patients with node-positive breast cancer, Bonadonna et al. demonstrated that patients who received ≥85% of the prescribed chemotherapy doses had a significant survival advantage compared to those who received less of the prescribed dose of CMF (cyclophosphamide, methotrexate, fluorouracil) (6). The importance of full-dose administration of chemotherapy to prevent disease progression has also been demonstrated in other studies of the treatment of node-positive breast cancer (7, 8).

Older women are less likely to receive treatment in concordance with guidelines for definitive surgery, adjuvant chemotherapy and adjuvant hormonal therapy (9). These findings are consistent with a study by DeMichele et al., which reported that the likelihood of receiving a recommendation in favor of chemotherapy were significantly decreased in women ≥70 compared to women from 50-59 years old (23% vs. 92%) (10). In a retrospective study of 407 patients older than 80 with breast cancer, Bouchardy et al. (11) showed that such patients are diagnosed at a later stage of the disease and are treated less frequently, in accordance with standardized guidelines. They found that only 47% of the older patients...
received standardized therapy, whereas 91% of the patients between 50 and 79 years old received such therapy. The 5-year survival rate of the untreated patients was 46%. Non-standardized therapy, such as the use of radiation treatment alone, showed no advantage over non-treatment. The specific 5-year survival rate of patients who only received tamoxifen was 51%. In comparison, older women who received conservative breast therapy and, in addition, an adjuvant therapy, had a specific 5-year survival rate of 90%. In this study, therefore, undertreatment was a prognostic factor for older patients (11). That avoiding undertreatment is associated with improved survival of women with breast cancer has also been demonstrated in a Canadian study about the impact of consensus guidelines for adjuvant systemic therapy (12).

Djordjevic et al. compared 1,334 patients <65 years old with 862 older breast cancer patients. Approximately 27% of the younger patients received adjuvant radiation therapy, as compared to 11% in the older subgroup. Similarly, significantly more of the younger patients received chemotherapy (30% vs. 9%, respectively). In both age groups, adjuvant endocrine therapy alone was given at approximately the same frequency (32% vs. 30%, respectively), although it must be noted that, in the retrospective analysis, significantly more older patients were estrogen-receptor-positive (68% vs. 28%, respectively). The proportion of patients in the younger group who died from breast cancer was 73%, as opposed to 81% in the older subpopulation (13). In contrast, Schairer et al. found that, with age, death from other causes became increasingly important. The probability of death from breast cancer in patients with localized disease was 33% lower among the oldest (≥70 years) compared with the youngest (<50 years) patients. On the other hand, patients with distant metastases died in the majority from breast cancer, regardless of age (14).

Muss et al. presented a sub-group analysis of 6,487 patients from the CALGB studies 7,581, 8,082, 8,541 and 9,344 for node-positive breast cancers, with respect to age and the effect of adjuvant chemotherapy. The median follow-up was 9.6 years, and the age distribution of the population was 54% below 50, 38% from 51-64 and only 8% who were 65 years old or more. The ≥65 group had significantly more positive lymph nodes. With respect to overall survival, the older patients had the same advantage from a higher dose chemotherapy as did the younger patients (15). With regard to the relative risk reduction of disease-free survival, the older patients benefited even more (response rate, RR, 31%) from a higher dosed chemotherapy in comparison with patients ≤50 years of age (RR 11%) (16). In this retrospective analysis, it could also be concluded that older patients are under-represented in clinical studies. Furthermore, the older patients had received chemotherapy only at an advanced stage of the disease as compared with younger subpopulations.

In the study by Gajdos et al., 920 patients ≥70 years old were compared with 206 older patients. This study confirmed that older patients are treated less aggressively with respect to therapeutic standards. Fewer older patients received adjuvant radiological therapy and/or chemotherapy; they received tamoxifen more frequently. The older patients’ local and distant recurrence rates were comparable to those of their younger counterparts. The absence of a significant impact of undertreatment with respect to disease-free survival in the elderly is probably due to the less aggressive biology of breast cancer in the elderly (5). In contrast, Bouchardy et al. determined no significant difference in the tumor biology between the younger patients and their older counterparts (11).

Dose-intensive chemotherapy – can it be used with older patients?

Additional developments in adjuvant chemotherapy may also improve survival in node-positive breast cancer, including the use of dose-dense, dose-intensive and sequential regimens (7, 8, 17). These regimens increase the amount of therapeutic agent that patients receive, using higher doses, shorter intervals between cycles or two different drug combinations in sequential cycles.

In spite of these advances, many older patients with breast cancer receive reduced quantities of chemotherapeutic agents because of reduced doses, delayed or missed cycles, or both. In a retrospective study of more than 20,000 patients, Lyman and colleagues found that patients aged ≥65 had a significantly greater risk of receiving a reduced relative dose-intensity compared to younger patients (odds ratio, 1.659; p<0.001) (18). A common reason for dose reductions and cycle delays was neutropenia, a significant dose-limiting toxicity of chemotherapy, for which the risk increases with age (18, 19). However, neutropenia can be managed using granulocyte colony-stimulating factors (G-CSFs), thereby increasing the safety and tolerability of both dose-dense and conventional regimens (8, 20). The effects of dose-dense regimens on patients ≥60 years of age with node-positive breast cancer have not been studied extensively and it is not known whether regimens appropriate for younger women are suitable for patients ≥60 years old.

The NOGGO (Nord Ostdeutsche Gesellschaft für Gynäkologische Onkologie – Northeast German Society of Gynecological Oncology) compared a dose-dense combination regimen containing epirubicin and paclitaxel in 14-day cycles followed by CMF with a conventional regimen with epirubicin and cyclophosphamide followed by CMF in patients with 4 or more positive lymph nodes (21). In a subgroup analysis, the feasibility, safety and tolerability of these two regimens for women aged ≥60 years in comparison with the same regimens in women aged <60 years were investigated. Of the 211
patients for whom age data were available, 52 (26%) were ≥60 years of age, including 25 out of 104 patients (24%) in the dose-dense schedule group and 27 out of 107 patients (27%) in the conventional schedule group. A total of 203 patients (96% in each age group) received all 7 chemotherapy cycles. Among patients aged ≥60 years, all the patients in the dose-dense schedule group and 24 (89%) of the conventional schedule patients received all 7 cycles of therapy. The safety and tolerability of the two regimens were similar between the two age groups, as assessed by discontinuation and interruption of therapy, laboratory values and hematological and non-hematological toxicity. For hematological toxicity, age was a factor in the frequency of Grades 3 and 4 leukopenia and neutropenia in both treatment groups. Those patients of ≥60 had more cycles with Grades 3 and 4 leukopenia (26% vs. 12%) and neutropenia (33% vs. 25%) compared to patients <60 years, respectively. No patients experienced Grade 4 anemia or Grade 4 thrombocytopenia, while Grade 3 anemia and thrombocytopenia were rare among patients of all ages in both treatment groups. Grade 3 or 4 non-hematological toxicities were rare and occurred at similar rates among patients in both age groups.

In summary, both regimens proved to be safe and tolerable, enabling the receipt of full doses of chemotherapy in 99% of cycles and the completion of all 7 cycles of chemotherapy by 96% of the patients in both age groups. Leukopenia and neutropenia occurred more frequently in the older patients, as did cycle delays. The use of filgrastim as a growth factor support in the first cycle for patients receiving dose-dense therapy appeared to reduce the incidence of leukopenia and neutropenia that could have been expected in a dose-dense regimen.

**Pharmacologically effective changes in older patients**

Between the second and eighth decades of life, the proportion of body fat increases by 35%, the volume of plasma decreases by 8% and the extracellular fluid decreases by 40%. These changes in the distribution of volume lead, for example, to increased cardiotoxicity of the anthracyclines (22). Existing anemia is an independent risk factor for myelo-toxicity and can lead to increased toxicity of, for example, anthracyclines and taxanes, due to their binding to erythrocytes. It should also be taken into account that renal output in older patients is significantly reduced. The activity of the oxidative mechanism by the cytochrome P450 as well as hepatic perfusion (blood flow) are also reduced, leading to reduced metabolism of the cytostatics (e.g., anthracyclines) in the liver (22).

**Conclusion**

A recent analysis in the United States showed that older patients comprise 61% of patients with malignant diseases, but only 32% of the patients in clinical phase II-III studies, with the under-representation being more pronounced in trials for early-stage than for late-stage cancers (23).

Various research groups have shown that older patients are frequently diagnosed with tumors in an advanced stage, which is, in part, due to the fact that they are often first examined when they show symptoms (24-26). Older patients frequently have a higher proportion of estrogen receptor-positive tumors and, in general, a less aggressive tumor biology (5, 13, 26). The advantage of adjuvant endocrine therapy with tamoxifen in hormone receptor-positive patients has been demonstrated by a meta-analysis carried out by the Early Breast Cancer Trialist’s Collaborative Group (27). To date, primary endocrine treatment alone is still widespread, being administered in 20% of patients between 65 and 79 years of age, and in more than 60% of patients over 80 years of age (data from the UK)(28). However, data from the five randomized trials of tamoxifen vs. surgery carried out in older women have demonstrated that solo endocrine therapy is of no advantage in older patients. As a result, primary endocrine therapy should only be administered to patients with metastases or to women with serious comorbidities, which do not allow surgical intervention (28).

The meta-analysis of the Early Breast Cancer Trialist’s Collaborative Group indicated a similar magnitude of response to adjuvant treatment in patients over 70, compared to those between 60 and 69, which, however, was not significant due to the small number of cases in this age group (28, 27). A study by the International Breast Cancer Study Group showed that older, estrogen receptor-negative patients benefitted from adjuvant chemotherapy even in lymph node-negative cases. Patients who were estrogen receptor-positive received no benefit from the additional administration of CMF to tamoxifen (29). The adjuvant treatment efficacy of tamoxifen plus epirubicin vs. tamoxifen alone in women age ≥65 years with node-positive breast cancer were evaluated in a phase III trial by the French Adjuvant Study Group 08. The 6-year disease-free survival rates were 69.3% with tamoxifen and 72.6% with epirubicin and tamoxifen. No overall survival advantage with the combination regimen was observed, considering the relatively short follow-up time of 6 years. A subset analysis showed that chemotherapy plus endocrine therapy was of advantage in hormone-receptor-negative patients (30).

To date, there has been a lack of valid data on the requirements for adequate therapy of breast cancer in older patients. The first evaluations of studies have shown that older patients suffering from breast cancer could also profit from treatment-satisfying therapeutic standards. Nonetheless, in light of the lower life expectancy, the higher comorbidity, as well as the changed biological status of aged patients, studies should be developed that address these specific conditions. The first moves in this direction are the recently inaugurated...
phase III studies of older women which have been initiated by various national and international research groups (e.g., the GBG, the German Breast Group, which is conducting the ICE Study, Ibandronate with or without Capecitabine in Elderly Patients; the CALGB, Cancer and Leukemia Group B-49907 Study; the Multicenter European Study, ACTION, Adjuvant Cytotoxic ChemoTherapy In Older WomeN).

References


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