NEW ASPECTS IN THE TREATMENT OF GYNECOLOGICAL CANCERS

Edited by
J. Sehouli and W. Lichtenegger

NOGGO Symposium, October 29, 2004
Seventh International Conference of Anticancer Research
October 25-30, 2004, Corfu, Greece

Organizing Committee:
J. Sehouli, E. Özcelik, D. Könsgen, A. Mustea

Sponsor:
North-Eastern German Society of Gynecological Oncology (www.NOGGO.de)

ANTICANCER RESEARCH *26*: 1673-1676 (2006)

Review

Chemotherapy Treatment Options for Elderly Women with Breast Cancer

SHERKO KÜMMEL[1], DIRK ELLING[3], SOPHIA JESCHKE[1], PETER SCHMID[2] and ANKE THOMAS[1]

Departments of [1]Senology and [2]Hematology and Oncology, University Medicine Berlin, Charité Campus Mitte, Berlin; [3]Department of Senology, Hospital Lichtenberg, Berlin, Germany

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 (e.g., dose-intensive chemotherapy) can be used with older patients. A common reason for dose reductions is neutropenia, but studies have shown that it is manageable by using granulocyte colony-stimulating factors (G-CSFs). In this review, the current status of clinical research in the area of adjuvant treatment and the necessity for clinical studies that take into account the special therapeutic requirements of older women are discussed.*

One of the main risk factors for the development of breast cancer is the general increase in age of the population (1). Despite this increase in life expectancy and the accompanying increased risk of developing breast cancer, there is only limited evidence-based data from randomized studies on the treatment of female breast cancer patients of advanced age. That older women, especially those over 70, have less aggressive tumors and a higher rate of co-morbidity has resulted in undertreatment of this subpopulation (2). In general, older women are excluded from clinical studies and are given less aggressive therapies (3-5).

Thus, two significant questions arise: whether undertreatment of older patients with breast cancer leads to a poorer prognosis and whether new therapy strategies, for example dose-intense 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

Correspondence to: Dr. med. Sherko Kümmel, University Medicine Berlin, Department of Senology, Charité Campus Mitte, Berlin, Schumannstr. 20/21, 10117 Berlin, Germany. Tel: +4930450564022, Fax: +49450564922, e-mail: sherko.kuemmel@charite.de

Key Words: Chemotherapy, breast cancer, elderly patients, review.

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 benefitted 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 (21).

Pharmacologically effective changes in older patients

Between the second and eigth 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

1 Armstrong K, Eisen A and Weber B: Assessing the risk of breast cancer. N Engl J Med *342*: 564-571, 2000.

2 Yancik R, Ganz PA, Varricchio CG *et al*: Perspectives on comorbidity and cancer in older patients: approaches to expand the knowledge base. J Clin Oncol *19*: 1147-1151, 2001.

3 Hutchins LF, Unger JM, Crowley JJ *et al*: Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med *341*: 2061-2067, 1999.

4 Mandelblatt JS, Hadley J, Kerner JF *et al*: Patterns of breast carcinoma treatment in older women: patient preference and clinical and physical influences. Cancer *89*: 561-573, 2000.

5 Gajdos C, Tartter PI, Bleiweiss IJ *et al*: The consequence of undertreating breast cancer in the elderly. J Am Coll Surg *192*: 698-707, 2001.

6 Bonadonna G, Valagussa P, Moliterni A *et al*: Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med *332*: 901-906, 1995.

7 Budman DR, Berry DA, Cirrincione CT *et al*: Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J Natl Cancer Inst *90*: 1205-1211, 1998.

8 Citron ML, Berry DA, Cirrincione C *et al*: Randomized trial of dose-dense *versus* conventionally scheduled and sequential *versus* concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol *21*: 1431-1439, 2003.

9 Giordano SH, Hortobagyi GN, Kau SW *et al*: Breast cancer treatment guidelines in older women. J Clin Oncol *23*: 783-791, 2005.

10 DeMichele A, Putt M, Zhang Y, Glick JH and Norman S: Older age predicts a decline in adjuvant chemotherapy recommendations for patients with breast carcinoma: evidence from a tertiary care cohort of chemotherapy-eligible patients. Cancer *97*: 2150-2159, 2003.

11 Bouchardy C, Rapiti E, Fioretta G *et al*: Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol *21*: 3580-3587, 2003.

12 Hebert-Croteau N, Brisson J, Latreille J *et al*: Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. J Clin Oncol *22*: 3685-3693, 2004.

13 Djordjevic N, Karanikolic A and Pesic M: Breast cancer in elderly women. Arch Gerontol Geriatr *39*: 291-299, 2004.

14 Schairer C, Mink PJ, Carroll L and Devesa SS: Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst *96*: 1311-1321, 2004.

15 Muss HB, Woolf S, Berry D, Cirrincione C, Weiss RB, Budman D, Wood WC, Henderson IC, Hudis C, Winer E, Cohen H, Wheeler J and Norton L: Cancer and Leukemia Group B: adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA *293*: 1073-1081, 2005.

16 Muss HB WS, Berry DA, Weiss RB, Budman DR, Wood WC, Henderson IC, Hudis C, Winer EP and Norton L: Older women with node positive (N+) breast cancer (BC) get similiar benefits from adjuvant chemotherapy (Adj.) as younger patients (pts): The Cancer and Leukemia Group B (CALGB) experience. ASCO. Proc Am Soc Clin Oncol, pp. 4, 2003.

17 Hudis C, Seidman A, Raptis G *et al*: Sequential adjuvant therapy: the Memorial Sloan-Kettering Cancer Center experience. Semin Oncol *23*: 58-64, 1996.

18 Lyman GH, Dale DC and Crawford J: Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol *21*: 4524-4531, 2003.

19 Link BK, Budd GT, Scott S *et al*: Delivering adjuvant chemotherapy to women with early-stage breast carcinoma: current patterns of care. Cancer *92*: 1354-1367, 2001.

20 Henderson IC, Berry DA, Demetri GD *et al*: Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol *21*: 976-983, 2003.

21 Kummel S, Krocker J, Kohls A *et al*: Dose-dense adjuvant chemotherapy for node-positive breast cancer in women 60 years and older: feasibility and tolerability in a subset of patients in a randomized trial. Crit Rev Oncol Hematol, in press, 2005.

22 Wedding U, Merkel U, Farker K *et al*: Oncologic pharmacotherapy of elderly patients. Internist (Berl) *44*: 977-985, 2003.

23 Lewis JH, Kilgore ML, Goldman DP *et al*: Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol *21*: 1383-1389, 2003.

24 Siahpush M and Singh GK: Sociodemographic variations in breast cancer screening behavior among Australian women: results from the 1995 National Health Survey. Prev Med *35*: 174-180, 2002.

25 Hillner BE, Penberthy L, Desch CE *et al*: Variation in staging and treatment of local and regional breast cancer in the elderly. Breast Cancer Res Treat *40*: 75-86, 1996.

26 Busch E, Kemeny M, Fremgen A *et al*: Patterns of breast cancer care in the elderly. Cancer *78*: 101-111, 1996.

27 Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet *365*: 1687-1717, 2005.

28 Wyld L, Garg DK, Kumar ID *et al*: Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. Br J Cancer *90*: 1486-1491, 2004.

29 International Breast Cancer Study Group: Endocrine responsiveness and tailoring adjuvant therapy for postmenopausal lymph node-negative breast cancer: a randomized trial. J Natl Cancer Inst *94*: 1054-1065, 2002.

30 Fargeot P, Bonneterre J, Roche H *et al*: Disease-free survival advantage of weekly epirubicin plus tamoxifen *versus* tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French Adjuvant Study Group 08 trial. J Clin Oncol *22*: 4622-4630, 2004.

Received September 1, 2005
Revised February 2, 2006
Accepted February 8, 2006