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**Adjuvant chemotherapy in young women
with breast cancer**

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Introduction

Adjuvant chemotherapy in operable breast cancer is a field that has not stopped evolving since 1976 when Bonadonna et al [1] observed a reduction in the risk of recurrence of breast cancer in women with positive axillary lymph nodes after having received a combination of cyclophosphamide, methotrexate and 5-fluorouracil. Later, anthracyclines and taxanes were incorporated into polychemotherapy regimens, and further improvements in terms of disease free-survival (DFS), overall survival (OS) and loco-regional control were obtained [2, 3]. Today, many different combinations of cytotoxic agents exist, but because of the lack of specific markers for response to individual chemotherapeutic agents, there are no clear indications to prefer one particular regimen over another in the setting of adjuvant chemotherapy [4].

Benefits of adjuvant chemotherapy in breast cancer

The last quinquennial meta-analysis of the Early Breast Cancer Trialists' Collaborative Group on adjuvant chemotherapy, which included overviews from 1985 to 2000, showed that being treated for approximately 6 months with an anthracycline-based polychemotherapy reduces the annual breast cancer death rate by approximately 38% in women younger than 50 years old, an effect that is largely independent of the use of tamoxifen, and estrogen receptor (ER) status, lymph node involvement, or other tumor characteristics. They also demonstrated that these benefits were significantly better than those obtained with a regimen of cyclophosphamide, methotrexate and 5-fluorouracil [5].

In the largest meta-analysis of randomized trials to date on the efficacy of incorporating taxanes into anthracycline-based regimens for early breast cancer, De Laurentiis et al [6] reported that taxane administration resulted in an absolute 5-year risk reduction of 5% for DFS, and 3% for OS in patients with high-risk early breast cancer, regardless of ER status, lymph node involvement, type of taxane, age, menopausal status and

administration schedule. Nevertheless, despite the advantages of adjuvant chemotherapy, the magnitude of the benefit is modest, and approximately 100 patients have to be treated to benefit only 3-5 of them [3]. In addition, adjuvant chemotherapy is associated with considerable adverse effects, such as cardiac, bone and hematologic toxicities. In younger women, gynecological adverse effects such as infertility and premature ovarian failure are of particular importance.

Benefits of adjuvant chemotherapy in young women with breast cancer

Young women are considered a unique group of breast cancer patients in terms of tumor biology and genetics. According to several studies, breast tumors in young women are often larger, have a higher tumor grade, mitotic rate, and lymphatic vascular invasion, increased expression of human epidermal growth factor receptor-2 (HER-2), and lower estrogen and progesterone receptor expression than those of their older counterparts [7, 8]. Altogether, these features contribute to the higher rates of loco-regional recurrences and worse prognosis observed in young patients [9, 10].

However, the amount of information on breast cancer in young women is limited. The fact that the incidence of breast cancer in women younger than 35 years is relatively low, representing approximately 11% of all breast cancer patients according to the latest (2002-2006) National Cancer Institute Surveillance, Epidemiology and End Results data (<http://seer.cancer.gov/statfacts/html/breast.html>), may be partly responsible for the underrepresentation of this age group in clinical trials.

Consequently, guidelines and recommendations on treatment approaches are generally derived from larger trials including women of different age groups, or retrospective studies involving small samples. Moreover, differences in the cut-off age for considering a woman as young further affects the interpretation of results. Because of this, at present it is not very clear whether young women should be treated

differently from older women [11], but what is certain is that young women seem to obtain especial benefit from adjuvant chemotherapy.

Kroman et al [12] conducted a study in 10356 women to evaluate if age at diagnosis was a negative prognostic factor in primary breast cancer, and how disease stage and the use of adjuvant chemotherapy influenced this association. Interestingly, they found that, compared with the other age groups included in the study (45-49, 40-44 and 35-39), women with low-risk breast cancer younger than 35 years who did not receive adjuvant chemotherapy were more than twice as likely to die as similarly treated older women. This increased risk remained when women were grouped according to the presence of node negative disease and by tumor size, and was not observed among women who did receive adjuvant chemotherapy. Their results indicate that in breast cancer, being younger can be considered itself a risk factor for increased mortality. Therefore, young age alone may also be regarded as an indication for adjuvant chemotherapy [12].

More recently, Beadle et al [13] sought to determine the impact of several loco-regional treatment strategies on loco-regional recurrence (LRR) in patients under 35 years of age. Patients were treated with one of three treatment strategies: breast-conserving surgery, mastectomy or mastectomy followed by adjuvant radiotherapy. Adjuvant chemotherapy, generally doxorubicin-based, and taxane-based in patients with positive lymph nodes, was administered according to clinical staging, physician discretion and patient preference. Univariate analysis showed that the use of adjuvant chemotherapy had a statistically significant impact on the rate of distant metastases in the entire population. Multivariate analysis showed that lack of adjuvant chemotherapy had a statistically significant impact on LRR rates, regardless of whether patients were treated with breast-conserving surgery or mastectomy. This effect was not noted in patients with stage II disease. In patients with stage III disease, lack of adjuvant chemotherapy was associated with a worse OS [13].

Besides confirming that young women with breast cancer have high rates of LRR, the data presented in this study supports considering the use of adjuvant chemotherapy in young patients with stage I disease at diagnosis until more definite data on appropriate selection criteria are collected [13].

Current recommendations for adjuvant chemotherapy in young women

Adjuvant chemotherapy is currently the standard of care for women with operable breast cancer. Nevertheless, important changes related to patient selection have been introduced in the latest St. Gallen Consensus [4]. Given the current state of knowledge of this disease, the classification of patients according to single independent risk factors, such as hormone receptor status, axillary node status, risk of recurrence, HER-2, and BRCA1/2 status, is no longer applicable. Tumors with low expression of ER, HER-2 overexpression and increased proliferation predict response to chemotherapy in general, not to specific agents. Only the categorization of patients as highly endocrine or incompletely endocrine responsive remains important for the selection of patients with ER positive tumors to receive chemotherapy [4].

According to the St. Gallen Consensus, adjuvant chemotherapy is definitely indicated in women with triple-negative disease who are at sufficient risk of relapse to justify its use, and in patients with HER-2 positive invasive breast cancer along with or before administration of trastuzumab [4].

It is generally accepted that patients with high expression of ER obtain less benefit from the addition of adjuvant chemotherapy than from endocrine therapy. Nevertheless, data presented by the International Breast Cancer Study Group on DFS and OS indicate that younger women (<35 years) with ER positive tumors have a significantly worse DFS than those with ER negative tumors (25% vs 47%, respectively; $p=0.014$). In contrast, results for younger and older premenopausal patients are similar if their tumors are classified as endocrine nonresponsive [14].

Therefore, the use of adjuvant chemotherapy, even in young women with endocrine-responsive tumors, seems to be justifiable.

Adverse effects of adjuvant chemotherapy in young women

Young women with breast cancer face special issues when discussing systemic therapeutic options for their disease, which include concerns about quality of life, fertility preservation and pregnancy [15]. Chemotherapy-induced amenorrhea (CIA) due to ovarian failure is a common adverse effect seen in cancer patients. The incidence of CIA ranges from 20% to 68%, although it is largely dependent on patient age at diagnosis, ovarian function at the time of treatment and cytotoxic regimen used [15-17]. Fortunately, in a large proportion of young patients, menses return after the treatment is stopped [15].

If ovarian failure and permanent CIA are a concern, several fertility preservation strategies can be offered to the patient. Unfortunately, reliable data are scarce, and the majority comes from non-randomized trials and observational studies. Some of the methods frequently used on young patients reported in these studies are ovarian protection with gonadotropin-releasing hormone agonists, embryo cryopreservation following *in vitro* fertilization, ovarian stimulation followed by oocyte cryopreservation, and ovarian tissue cryopreservation [18]. It should be kept in mind that each technique carries potential disadvantages that must be weighed against the advantages [15].

Conclusions

The issue of whether young women with breast cancer should be treated differently from older women is a matter of debate, partly because of the lack of randomized trials comparing different strategies in this age group. Nevertheless, because existing data indicate that overall young women have a worse prognosis and clinical outcome, they

seem to obtain especial benefit from adjuvant chemotherapy. Currently, no single independent risk factor should be used to guide patient selection, although determination of hormone receptor status remains important. In this particular group of patients, the effects of adjuvant chemotherapy on fertility and ovarian function, as well as the available fertility-preserving strategies, must be openly discussed with the patient to minimize the impact on quality of life.

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