Adjuvant Chemotherapy for Young Women with Endocrine Non-responsive Early Breast Cancer: Any Issues?

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Introduction

Approximately 25% of newly diagnosed invasive breast cancer occurs in premenopausal women, with less than 10% of patients being less than 40 years of age at diagnosis [1].

The clinical behavior of breast cancer in younger women tends to be more aggressive than in older patients. Specifically, tumors in younger women present a higher grade and have a higher proliferating fraction and more vascular invasion than those occurring in older patients. Moreover, a higher proportion of patients are affected by tumors that do not express estrogen or progesterone receptors, while HER2 expression is apparently not influenced by age [2].

A review of the National Cancer Data Base reveals that patients younger than 35 years of age have more advanced disease at diagnosis and a poorer 5-year survival than older premenopausal patients. Similar findings have been reported from the National Cancer Institute SEER1 database, from the Finnish Cancer Registry, from the Southwest Oncology Group (SWOG) database, as well as from several studies described from single centers [3].

In early breast cancer, adjuvant treatment is decided according to risk and biological factors expressed on tumor cell surface. Guidelines from consensus conferences categorize patients in different groups and suggest treatment accordingly. For example, the 2007 St Gallen consensus meeting acknowledged 3 categories of tumors: highly endocrine responsive, incompletely endocrine responsive and endocrine non responsive tumors [4]. Each category is further divided into HER2 positive or HER 2 negative, to assign Transtuzumab treatment.
Aim of this short review is to discuss treatments and related issues in young patients with early breast cancer, with a specific focus on endocrine non responsive tumors.

Adjuvant treatment of young, endocrine non-responsive HER2 positive patients

In patients with HER2 positive tumors, the use of adjuvant trastuzumab has become the standard of treatment since the publication of a pooled analysis of the 3 randomized clinical trials which demonstrated a 52% reduction in tumor recurrence, corresponding to a 17% increase in 4 years disease free survival (DFS). Moreover, a benefit in overall survival (OS) was also described, with a relative risk reduction of 33% (p=0.015). Importantly, the improvement in DFS and OS was observed for all subgroup of patients, including those of younger age [5]. Also the HERA trial confirmed the significant improvement, both for DFS and for OS, even if trastuzumab was given sequentially [6]. Again the advantage of trastuzumab administration was irrespective of patient's age. Other schedules and combination are now under investigations, and the results of the extended trastuzumab schedule (2 years) are eagerly awaited. Moreover new molecular studies will help in selecting patients where the potentially more cardiotoxic anthracycline combination will give better results compared to non-anthracycline containing regimens.

Adjuvant treatment of young, endocrine non-responsive HER2 negative patients

Chemotherapy appears to be more effective for women younger than 50 years of age. Although this message is clearly given by the Early Breast Cancer Collaborative Trial (EBCCT) overview of most available randomized trials, it is not universally confirmed by individual large randomized studies [7]. Nonetheless, in young breast cancer patients with HER2 negative, endocrine non-responsive tumors, chemotherapy alone remains the treatment of choice. Recent molecular and immunohistochemical evidences identify patients affected by tumors which have a so called "basal type signature", with a gene expression profile similar to those tumors occurring in BRCA1 mutated patients. These tumors do not express ER, PgR or HER 2 and are usually referred to as "triple negative" tumors. Triple negative tumors have a worse prognosis when compared to other histologies occurring in young women and new clinical trials with antiangiogenetic strategies are ongoing [8]. The use of platinum compounds or alkylating agents, which act through direct DNA damage, is warranted by some investigators, but data are controversial [9].

Time to treatment start

The proper time to commence adjuvant chemotherapy after primary surgery for breast cancer is unknown. The International Breast Cancer Study Group (IBCSG)

investigated the relationship between early initiation of adjuvant chemotherapy, ER status, and prognosis in 1,788 premenopausal, node-positive patients treated with classical CMF as adjuvant chemotherapy [10]. Among patients with ER-absent tumors, the 10-years DFS was 60% for the early initiation group (within 3 weeks from surgery) compared with 34% for the conventional initiation group (HR 0.49; 95% CI, 0.33 to 0.72; P= 0.0003). The results of this study show that premenopausal patients with ER-absent tumors and patients with tumors expressing some ER represent distinct populations with respect to responsiveness to early commencement of adjuvant chemotherapy. It should be pointed out, though, that subsequent retrospective analysis did not completely confirm these findings.

Fertility issues in young patients receiving chemotherapy

Fertility issues are of utmost importance in young patients with breast cancer. In a recently published retrospective analysis, 57% of women were seriously worried about chemotherapy induced infertility, and this influenced treatment decision in 29% of women [11].

Age at diagnosis, use of alkylating agents and cumulative chemotherapy dose are the most relevant factors which can predict the occurrence of chemotherapy related amenorrhea and infertility [12]. Even if amenorrhea could be useful for young women with endocrine responsive tumors, low estrogens levels are associated with severe impairment of quality of life. Premature ovarian failure is associated with somatic symptoms (hot flushes, vaginal dryness, premature osteoporosis) and psychological symptoms (reduction of libido and self esteem, sleep disorders) which alter body image and relationships.

New strategies of fertility preservation before chemotherapy are then warranted, including embryo freezing, egg freezing, oocyte in vitro maturation and ovarian freezing. Moreover trials with LHRH agonists or antagonists to protect the ovaries during chemotherapy are ongoing. Notably, most observational studies of pregnancy following breast cancer are reassuring and do not suggest that this carries a risk of higher breast cancer recurrence or death.

In conclusion, adjuvant chemotherapy with or without trastuzumab remains the main treatment modality for young women affected by endocrine non-responsive early breast cancer. Ongoing clinical trials will possibly ameliorate prognosis with more attention to quality of life issues in this special patient's population.

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