Benefits and adverse effects of endocrine therapy

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Endocrine-responsive tumors that are small and without nodal involvement (i.e. tumors classified as pT1 pN0) are a heterogeneous group of tumors that are associated with a low risk of relapse in the majority of the cases. Therefore, the costs and benefits of adjuvant endocrine therapy should be carefully considered within this subgroup of patients. Treatment decisions should take into consideration co-morbidities as well as the presence of other classical risk factors such as HER2 overexpression or extensive peritumoral vascular invasion. Tamoxifen or tamoxifen plus ovarian function suppression should be considered as proper endocrine therapies in premenopausal patients. Ovarian function suppression alone or ovarian ablation might also be considered adequate in selected patients (e.g. very low-risk patients, in the presence of co-morbidities or patient preference). An aromatase inhibitor should form part of standard endocrine therapy for most postmenopausal women with receptor-positive breast cancer, although patients at low risk or with co-morbid musculoskeletal or cardiovascular risk factors may be considered suitable for tamoxifen alone. Tailored endocrine treatments should be considered in patients with endocrine-responsive tumors classified as pT1 pN0. Issues focusing on safety, quality of life and subjective side effects should be routinely discussed.

Key words: adjuvant treatment, early breast cancer, endocrine therapy, side effects

Introduction

Care for patients with breast cancer tends toward more selective interventions to minimize acute and late toxicity without compromising efficacy. In particular, for the subgroup of patients with tumors ≤2 cm in size that do not have nodal involvement (i.e. tumors classified as pT1 pN0), appropriate adjuvant systemic therapy involves choosing treatments tailored to individual patients according to assessments of patient risk, co-morbidities and preference [1–3]. Although nodal status remains the most important feature for defining risk category, several classical risk factors should be considered within the subgroup of patients with pT1 pN0 disease [2]. Features which might indicate increased risk of recurrence include extensive peritumoral vascular invasion [4, 5], or amplification or overexpression of HER2 [6]. The presence of high grade and/or a high proliferation index might also identify a subgroup of patients with a higher risk of relapse [7]. Finally, young age should also be taken into consideration, due to its negative prognostic role and to the differing response by age to systemic therapy when compared with older, premenopausal patients with breast cancer [8, 9].

It is the intention of this report to discuss the evolving knowledge of adjuvant endocrine treatments in order to define reasonable treatment strategies in patients with small tumors and node-negative disease.
Tamoxifen has been associated with augmented bone mineral density (BMD) in postmenopausal women treated for breast cancer, but with decreased BMD in premenopausal women [24]. The drug has been shown to decrease low-density lipoprotein and total cholesterol in postmenopausal women [25], with the effect maintained during 5 years of treatment [26]. Despite the favorable effect of tamoxifen on lipid profiles, a meta-analysis of tamoxifen trials showed no effect on the

**tamoxifen**

Tamoxifen, which inhibits the activity of estrogen by competitively binding to the ER, continues to be an important component of adjuvant treatment for patients with tumors that express steroid hormone receptors. Treatment with 5 years of tamoxifen has been shown to be effective for reducing the risk of recurrent disease and death in premenopausal and postmenopausal women with hormone-responsive breast cancer [12]. In particular, for patients with ER-positive disease, 5 years of adjuvant tamoxifen reduced the annual breast cancer death rate by 31% [12]. The proportional risk reductions of recurrence and mortality produced by tamoxifen were little affected by age or by nodal status. Conversely, the absolute risk reduction of recurrence after 5 years of tamoxifen was significantly greater for those with node-positive than node-negative disease (16.1% versus 9.1%). For breast cancer mortality, the 10-year gains in terms of absolute risk reduction of mortality were substantial for those patients with node-negative disease (12.2% versus 17.5%, 10-year gain 5.3%, \( P < 0.00001 \)) [12].

Several major trials, focusing on the node-negative population, evaluated the use of tamoxifen as a single agent compared with no adjuvant therapy. The NSABP B-14 study demonstrated that compared with placebo, tamoxifen benefited women through 5 years of adjuvant tamoxifen versus placebo [19]. Compared with placebo, tamoxifen benefited women through 15 years, irrespective of age, nodal status, or tumor ER concentration [hazard ratio (HR) for recurrence-free survival 0.58, 95% CI 0.50–0.67, \( P < 0.0001; HR \) for overall survival 0.80, 95% CI 0.71–0.91, \( P = 0.0008 \)]. Multivariate analyses presented in their first report indicated benefit for subgroups defined by age, tumor status, clinical tumor size and type of operation [19].

The Scottish Adjuvant Tamoxifen (SAT) trial assessed the effect of tamoxifen given to patients with breast cancer (i) immediately after surgery or (ii) only after the patient had a relapse. The majority of the 1322 women enrolled were postmenopausal, although node-negative premenopausal women were allowed. Tumor tissue from approximately half the women was assessed for expression of ER. As with NSABP B-14, significant improvements in disease-free and overall survival were observed [20]. Updated results of the SAT trial, after a median follow-up of 15 years, showed a continued beneficial effect of 5 years of adjuvant tamoxifen on the probabilities of overall survival (\( P = 0.006 \)), systemic relapse (\( P = 0.007 \)) and death from breast cancer (\( P = 0.002 \)) [21]. Because of the small subgroup size, no definitive conclusions could be drawn about the treatment effects in patients with node-negative disease.

As initially reported in the NSABP B-14 study, the most common toxicity that led to discontinuation of tamoxifen was hot flushes [19]. Other side effects included vaginal discharge, irregular menses and thromboembolic events. It is now well established that, when compared with placebo, tamoxifen treatment is associated with an increased incidence of vaginal bleeding, endometrial polyps, endometrial thickening and ovarian cysts [22]. In particular, a meta-analysis conducted on 23 trials with 45 936 patients reported that tamoxifen was associated with a statistically significant increase in endometrial cancer risk [relative risk (RR) 2.70; 95% CI 1.94–3.75] [23]. When women who were postmenopausal or in treatment trials were considered separately, risk increases were greater [23]. Results from a meta-analysis conducted on 32 trials (52 929 patients) indicated that tamoxifen was associated with a statistically significantly increased risk of stroke, with an RR of 1.49 (95% CI 1.16–1.90) [23]. The drug was also associated with a significantly increased risk of pulmonary emboli (RR 1.88; 95% CI 1.17–3.01) as well as an increased incidence of deep venous thromboses (RR 1.87; 95% CI 1.33–2.64) [23].

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incidence of myocardial infarction (MI) (RR 0.90; 95% CI 0.66–1.23), although death from MI was significantly decreased in women likely to have hyperlipidemia and coronary artery disease (RR 0.62; 95% CI 0.41–0.93) [23]. Although an advantage from the use of tamoxifen can be demonstrated for patients with lower risk disease, the question of whether or not to treat with tamoxifen depends on a risk–benefit analysis. The low relapse rate within the first 10 years and the potential reductions in risks of recurrence of breast cancer in the conserved breast or in the contralateral breast should be taken into account and weighed against risks of endocrine treatment.

combined endocrine therapy with tamoxifen plus ovarian suppression

One of the most relevant questions remaining is whether or not premenopausal patients should be offered tamoxifen alone or tamoxifen plus ovarian suppression. Data from randomized trials in advanced disease indicate that the combination of tamoxifen and a GnRH analog might be more effective than each of the modalities alone [27]. Despite the lack of conclusive data favoring the combination of tamoxifen plus ovarian function suppression in the adjuvant setting, this combination might be considered reasonable for selected groups of patients, such as very young patients or those with HER2-positive disease. In fact, very young patients have a worse prognosis compared with older premenopausal women presenting with otherwise similar cancer [28]. Moreover, it has been shown that chemotherapy alone is insufficient for younger patients with steroid hormone receptor-positive tumors, perhaps because cytotoxic regimens do not effectively suppress ovarian function in this age group [29].

Combined adjuvant endocrine therapy (oophorectomy in combination with tamoxifen) has been compared with the same endocrine therapy at the time of recurrence in 709 premenopausal patients. The combination of bilateral oophorectomy followed by tamoxifen was effective when compared with no adjuvant treatment, even among patients with tumors overexpressing HER2 [30].

aromatase inhibitors

Aromatase inhibitors (AIs) block the conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma [31]. Third-generation AIs include the non-steroidal inhibitors, letrozole and anastrozole, and the steroidal inhibitor, exemestane. Recent reports of large trials conducted in the adjuvant setting indicate better outcomes among women given AIs than among those given tamoxifen. In particular, initial adjuvant endocrine therapy with anastrozole or letrozole was found to reduce the risk of relapse significantly among postmenopausal women with endocrine-responsive disease when compared with tamoxifen [32, 33]. Also, sequential endocrine therapy using exemestane or anastrozole after 2–3 years of tamoxifen to complete 5 years of adjuvant endocrine therapy significantly improved treatment outcome [34, 35]. A meta-analysis of randomized trials of AIs compared with tamoxifen either as initial monotherapy or after 2–3 years of tamoxifen was recently published and confirmed that AIs produce significantly lower recurrence rates compared with tamoxifen either as initial monotherapy or after 2–3 years of tamoxifen [36]. In subgroup analyses of recurrence, there was not apparent heterogeneity in the proportional recurrence reduction with respect to nodal status.

However, limited information is available specifically for the subgroup of patients with pT1 pN0 tumors. The Breast International Group (BIG) 1-98 study compared letrozole monotherapy with tamoxifen monotherapy as initial adjuvant endocrine therapy, as well as the sequential treatment with the two agents in either order in postmenopausal women with hormone receptor-positive breast cancer [33]. Exploratory analyses were recently conducted on a cohort of 2960 women in BIG 1-98 with small tumors and node-negative disease (pT1 pN0). In an intention-to-treat analysis of 5 years of monotherapy with either tamoxifen or letrozole, there was no difference in 5-year disease-free survival between patients assigned to tamoxifen (91.2%; 95% CI 89.2% to 92.9%) compared with those assigned to letrozole (91.2%; 95% CI 89.1% to 92.9%), nor was there a difference between treatments with respect to 5-year overall survival (tamoxifen, 96.5%; 95% CI 95.1% to 97.6%; letrozole, 96.4%; 95% CI 94.9% to 97.5%). The results were consistent when follow-up of the women who selectively crossed from tamoxifen to letrozole was truncated at the time of selective crossover.

The profile of side effects between AIs and tamoxifen is different in published trials. There was a higher incidence of thromboembolic events among women who were assigned to tamoxifen than among those who were assigned to an AI [37]. Also, the incidence of hypercholesterolemia (predominantly mild) was lower among women who were assigned to tamoxifen than among those who were assigned to an AI [37]. Vaginal bleeding and hot flushes were reported more frequently in women who were assigned to tamoxifen than in those who were assigned an AI [37]. There were similar rates of stroke and transient cerebral ischemic attacks between women who were assigned to tamoxifen and those who were treated with an AI although, in the ATAC trial, anastrozole was associated with a lower incidence of cerebrovascular events than was tamoxifen [32]. The incidence of cardiac events of any type or grade was similar between women who were assigned to one of the regimens that included letrozole and women who were assigned to tamoxifen monotherapy in the BIG 1-98 trial (6.1–7.0% and 5.7%, respectively; P = 0.45) [33]. However, in the monotherapy arms in the BIG 1-98 trial, a non-statistically significant trend toward a greater incidence of ischemic heart disease was observed for patients assigned to letrozole (2.8% versus 2.0%, P = 0.08) [33]. In the IES trial, in which women were switched from tamoxifen to exemestane after 2–3 years, there was a non-statistically significant trend toward an increase in the incidence of myocardial infarction with tamoxifen (1% versus 0.4%) [34]. In the ATAC study, no significant difference in the incidence of cardiovascular disease was reported between women treated with anastrozole and those treated with tamoxifen. Arthralgia, myalgia or both were more frequent, in general, among women assigned to an AI than among women assigned to tamoxifen [32, 37].

The incidence of fractures was higher among women assigned to an AI compared with women assigned to tamoxifen.
In particular, in the BIG 1-98 study, the incidence of fractures was highest among women assigned to letrozole monotherapy and lowest among women assigned to tamoxifen monotherapy (10% versus 6.7%; P <0.001) [35].

Estrogen deprivation might lead to some impairment of cognitive function. Tamoxifen may adversely affect cognition [38], although few investigations on this specific side effect have been conducted. Recently, it has been shown that after 1 year of adjuvant therapy, tamoxifen use was associated with statistically significantly lower functioning in verbal memory and executive functioning when compared with healthy controls. In contrast, exemestane use was not associated with lower cognitive functioning [39]. Using data from the BIG 1-98 trial, patients taking adjuvant letrozole during the fifth year of treatment had better cognitive functioning than those taking tamoxifen [40].

Since the profiles of adverse events for AIs and tamoxifen differ, patients should be evaluated for baseline co-morbidities and monitored during treatment. Quality-of-life issues related to endocrine therapies, which might affect their acceptance, should also guide in the selection of endocrine therapies in postmenopausal patients. Future trials should evaluate how to reduce side effects and thus improve tolerance [41]. In the meanwhile, for patients at low risk of relapse or with co-morbidities that raise concern about the safety of AIs, adjuvant tamoxifen alone remains a reasonable alternative, and may be an economically viable option in many situations.

disclosures

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references

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