

educational session

Adjuvant treatment of breast cancer

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sequence and duration of hormonal therapy

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trastuzumab in adjuvant setting

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Adjuvant treatment of breast cancer: sequence and duration of hormonal therapy

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introduction

The role of hormones in the treatment of breast cancer has been recognized for more than a century, since Beatson published his observations on the effect of oophorectomy in patients with metastatic breast cancer in 1896 [1].

In the adjuvant setting the role of hormonal responsiveness and of hormonal treatments has been re-emphasized during the last Consensus Conference held in St. Gallen, Switzerland (Table 1) in 2005 [2]. However, important questions regarding selection of the hormonal manipulation, duration of the hormonal treatment and the best sequence of different hormones are still open and will be discussed.

pre-menopausal women

In pre-menopausal patients ovarian ablation or ovarian function suppression and tamoxifen have been investigated and their role in the adjuvant setting for patients with expression of hormone receptors on their tumors has been established.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview published in 1996 and updated in 2005 showed that this treatment approach resulted in a $25\% \pm 7\%$ reduction in recurrences and a $24\% \pm 7\%$ reduction in mortality compared with women who received no treatment (15-year disease-free survival (DFS) 45.0% versus 39.0% and overall survival (OS) 52.4% versus 46.1%) [3]. Ovarian ablation has shown to yield similar results as chemotherapy (cyclophosphamide-methotrexate-5-fluorouracil (CMF) schedule) in patients with hormone receptor expressing tumors [4].

The role of ovarian ablation in patients receiving adjuvant chemotherapy is still controversial since most of the trials did not show significant benefits for this approach. This may be due to the fact that in most patients, in particular if older than 40 years, chemotherapy alone is causing a permanent amenorrhea in a large percentage of women [5, 6]. The addition of ovarian ablation has been however shown to be beneficial for young patients that are less likely to develop an ovarian failure with chemotherapy alone [7].

The optimal duration of tamoxifen is currently considered to be 5 years. Undoubtedly less clear is the duration of a luteinizing hormone-releasing hormone (LH-RH) analogs therapy. Most of the trials have investigated 2, 3, or 5 years treatments but the optimal duration has not been assessed.

Tamoxifen has been extensively used either alone or in combination with ovarian ablation or with chemotherapy. The report from the EBCTCG [3] published in 2005 shows after 15 years of follow-up, that 5 years of tamoxifen treatment produced an $11.8\% \pm 1.3\%$ absolute reduction in breast cancer recurrence and a $9.2\% \pm 1.2\%$ reduction in breast cancer mortality in women with estrogen receptor (ER)-positive tumors. The absolute improvement in breast cancer mortality associated with tamoxifen was $12.6\% \pm 2.0\%$ for women with lymph node-positive disease and $5.3\% \pm 0.9\%$ for women with node-negative disease regardless of age, adjuvant chemotherapy, or tamoxifen dose. The reduction in both recurrence and mortality was significantly higher in women who had 5 years of adjuvant tamoxifen therapy compared with those who received only 1 to 2 years. In addition a 50% reduction in the rate of contralateral breast cancer was observed among tamoxifen treated women with ER-positive or ER-unknown breast cancer. Patients with ER-negative disease receiving tamoxifen did not show a significant difference in recurrence or mortality rates.

The combination of ovarian ablation and tamoxifen has been investigated in the metastatic setting and has proven superior to LH-RH analogs alone [8]. Whether this observation is also true in the adjuvant setting is currently investigated in clinical trials [9].

Some trials further investigated the value of adjuvant tamoxifen therapy beyond 5 years, although the small trials completed thus far have not demonstrated any benefit and the NSABP trial even showed a possible detrimental effect of prolonged tamoxifen [10].

The addition of chemotherapy to tamoxifen produces additional benefits and similarly tamoxifen added to the benefits of chemotherapy [10, 11, 12].

Tamoxifen can be associated with severe side effects, like thrombo-embolism, development of endometrial cancer and possibly osteoporosis in pre-menopausal patients [13]. The use of aromatase inhibitors that have proven superiority to tamoxifen and a different toxicity profile is currently investigated in this population in trials of the International Breast Cancer Study Group conducted globally within the context of the Breast International Group (BIG) and partially of the American Intergroup [9]. Long-term toxicity will however continue to be a concern in this population and will need to be carefully evaluated.

post-menopausal women

Tamoxifen or other selective ER modulators (SERMS), like Toremifen [14], have been considered standard treatment for post-menopausal patients with hormone-receptor expressing tumors, both node-negative and node-positive.

Recently, large clinical trials involving several thousands of patients have shown a superiority of third generation aromatase inhibitors (AI) (anastrozole, letrozole and exemestane) used either up-front (anastrozole-ATAC and letrozole-BIG 1–98 trials), in sequence after 2–3 years of tamoxifen (exemestane-IES, anastrozole-ABCSG8/ARNO-95 and anastrozole-ITA trials), or in sequence after completion of 5 years of tamoxifen (letrozole-NCIC MA17) in terms of DFS compared to tamoxifen or placebo (NCIC MA17 trial) (Figure 1) [15–20].

AI have a different toxicity profile compared to tamoxifen. The data of the oldest AI trial, the ATAC, with a median follow-up of 68 months, show a significant increase of

arthralgia and of bone fractures for patients treated with AI and as expected significantly more endometrial cancers and thrombo-embolic events with tamoxifen [15].

The data of the IES and in particular of the BIG 1–98 trial raise concerns in terms of cardiovascular events related to the use of AI. The long-term toxicity of all AI needs to be carefully evaluated in all large trials that compared these compounds to either tamoxifen or placebo in order to really assess the risk-benefit ratio for this expensive therapy.

Several questions remain open for the use of AI in postmenopausal patients:

- Should AI be used up-front in the post-operative phase?
- Should AI be used only after 2–3 or 5 years of tamoxifen due to toxicity and economical considerations?
- Which is the optimal sequence? Tamoxifen followed by AI or AI followed by Tamoxifen (investigated in the BIG 1–98 trial)?

Table 1. Hormonal treatment of hormone receptor expressing breast cancer: St. Gallen 2005 [2]

	Premenopausal patients	Postmenopausal patients
Low risk	Tamoxifen or GnRH analogs or Nil	Tamoxifen or Aromatase inhibitors or Nil
Intermediate risk	Tamoxifen ± Ovarian function suppression* (± Chemotherapy) or Chemotherapy → Tamoxifen (± Ovarian function suppression or Tamoxifen or Ovarian function suppression	Tamoxifen or Aromatase inhibitors or Chemotherapy → Tamoxifen or Chemotherapy → Aromatase inhibitors (Indication for inclusion of an aromatase inhibitor in the treatment after 2–3 years or after 5 years of tamoxifen)
High risk***	Chemotherapy → Tamoxifen or Chemotherapy → Tamoxifen + Ovarian function suppression or Chemotherapy → (Aromatase inhibitors + Ovarian function suppression)**	Chemotherapy → Tamoxifen or Chemotherapy → Aromatase inhibitors (Indication for inclusion of an aromatase inhibitor in the treatment after 2–3 years or after 5 years of tamoxifen)

*Ovarian function suppression either by GnRH analogs or by surgical oophorectomy or by radiotherapy.

**No data available on the need to give chemotherapy and aromatase inhibitors in sequence. Tamoxifen should be given only after completion of chemotherapy.

***Trastuzumab to be discussed for patients with HER2 expressing tumors.

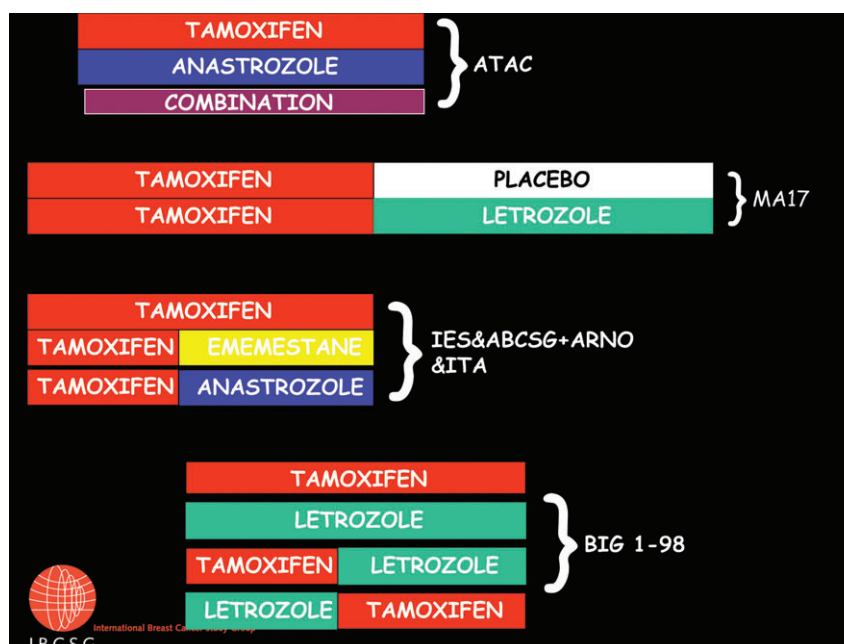


Figure 1. Trials of taxomifen and aromatase inhibitors.

- How long should AI be given? 5 years or more (currently investigated in the extension of the NCIC MA17 trial)?
- Which interval between the end of tamoxifen treatment and the beginning of AI therapy is optimal?
- Long-term toxicity of AI?

conclusions

In pre-menopausal patients the role of an oophorectomy and of tamoxifen has been established. The possible benefit of the combination of both or of the use of AI (obviously accompanied by a chemical castration) has still to be confirmed in this population and is currently investigated in ongoing clinical trials. The duration of the hormonal treatment in pre-menopausal patients has not been clearly defined. Different treatment durations, 2, 3 or 5 years, have been investigated and individual issues like recurrence risk but also personal wishes (e.g. fertility) have to be included in the discussion about duration of adjuvant therapy in young patients.

In post-menopausal women, AI have proven superior to tamoxifen in all large published trials. AI for 5 years are superior to tamoxifen, but also 2–3 years of AI after 2–3 years of tamoxifen have shown a benefit as compared to tamoxifen alone. The addition of 5 years (or more, under investigation) of AI after completion of 5 years of tamoxifen have shown a decrease of recurrence and an increase in survival in the ER positive-population which is more likely to have late recurrences. A prolongation of the duration of tamoxifen of more than 5 years has not proven to be beneficial and cannot be recommended.

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