E9. Update on systemic adjuvant treatment

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Breast cancer is still the most frequently diagnosed cancer in women in the Western World and the cause of a large amount of suffering.

Breast cancer is generally diagnosed in an early phase, when only a primary tumour and in 50–80% of cases (depending on the availability of early detection screening methods) ipsilateral axillary lymph node metastases are diagnosed. Despite adequate treatment, a number of patients will recur, possibly because of micro-metastases that are already present at diagnosis, but clinically undetectable. These develop into a metastatic spread during the follow-up of their disease. Nowadays, patients with metastatic disease are still considered incurable.

Systemic adjuvant treatment consisting of endocrine manipulations, chemotherapy, or a combination of both has been shown to decrease the number of recurrences and reduce mortality rates of early breast cancer patients. However, several issues still need to be addressed as despite a widespread use of these therapies too many women will recur and continue to die of their metastatic disease, demonstrating the urgent need for improvements.

Several strategies have been implemented to improve our knowledge and increase our understanding of the large amount of data that is available on systemic adjuvant treatment in breast cancer:

The National Institutes of Health (NIH) Consensus Conference on Adjuvant Therapy for Breast Cancer some years ago and the last St. Gallen International Consensus Conference in early 2003 resulted in the release of treatment guidelines in specific patients populations from an expert panel.

In addition to these conferences, the Oxford Overview provides additional evidence, although methodologically, it provides only average estimations of treatment benefits in the global population studied.

Recent data show that the dissemination of results from large clinical trials on adjuvant therapies is quite rapid allowing patients to profit from new knowledge after fairly short intervals [1].

In this paper, we will focus on postoperative adjuvant treatments. Due to space limitations, selected items can be discussed.

Treatment decisions are taken based on several factors related to the patient, to their tumour and to the available resources and after defining the risk of recurrence. The last St. Gallen Consensus guidelines propose decisions should be made based on the endocrine responsiveness of the disease that has been shown to be the most important predictive factor for response to endocrine manipulations. Patients with tumours expressing oestrogen and/or progesterone receptors have been shown to benefit from endocrine manipulations, whereas such treatments do not decrease the number of recurrences in hormone non-responsive diseases.

Endocrine therapy

Endocrine therapy has been used as treatment for breast cancer for more than a century, but several questions remain unanswered:

In premenopausal patients, a role for ovarian ablation alone has been shown in the Oxford Overview [2] and new trials in the adjuvant setting are examining the role of combined endocrine therapies (Ovarian ablation and tamoxifen, ovarian ablation and aromatase inhibitors), for which, at least in the metastatic disease, there seems to be an advantage in progression-free survival over each component given alone [3].

In the postmenopausal population, the aromatase inhibitor, anastrozole, has been shown to be superior to tamoxifen, and to the combination of tamoxifen and anastrozole. However, data on the long-term toxicity of these compounds (effect on bone mineral density, on blood lipids, on cognitive functions, for example) are still insufficient to draw firm conclusions on their risk-benefit and to definitively position the different therapies in the armamentarium of the adjuvant setting [4].

The recently published trial MA17 by the Canadian Group showed a large benefit for 5 years of another aromatase inhibitor (letrozole) given in recurrence-free patients after completion of 5 years of tamoxifen. These data are also too premature (median follow-up at publication of 2.4 years) to define the role of this treatment option. Only a small number of patients have completed the 5 years of additional treatment and are therefore generating information on long-term toxicities [5]. Two other large trials, including several thousand patients, are in the follow-up phase and will soon be published: The Exemestane trial examining the role of the steroidal aromatase-inhibitor, exemestane, given in sequence with

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tamoxifen and the Breast International Group (BIG) 1-98 trial comparing tamoxifen alone to letrozole alone and to the sequences of both compounds.

Chemotherapy

During the last decade, the taxanes have been used in the adjuvant as well as metastatic setting.

Several large trials have shown a benefit for patients that have received taxanes. However, in some of the trials, the benefit has been limited to a subpopulation of patients with oestrogen-receptor-negative disease.

High dose treatments: After publication of the rather disappointing results from randomised clinical trials [6,7] and the deceptions have been employed, enthusiasm for this treatment approach has waned and the procedure has been largely abandoned. Possibly, as shown by data from the International Breast Cancer Study Group (ex-Ludwig Group) (IBCSG) Trial 15, some selected subpopulations of breast cancer patients may benefit from this treatment, but it can no longer be recommended for general use.

Low dose treatments: New data have been published in metastatic disease on the role of metronomic low dose (anti-angiogenic?) chemotherapy. Data in patients with metastatic disease show encouraging results and a clinical trial is ongoing in hormone-receptor-negative patients.

Sequence of the different modalities: The role of sequencing of chemo- and endocrine therapy in the adjuvant setting has been shown to be relevant in the trial presented by Albain at the last St. Gallen Conference [8]. The concomitant use of chemo-endocrine therapy showed a significant disadvantage in disease-free survival compared with the sequential use of both modalities.

Combination of chemo-endocrine therapy

The use of combination chemo-endocrine therapy has been the subject of some clinical trials that have shown controversial results that may be interpreted in different ways. The trials of the IBCSG in a node-negative population, both pre- and postmenopausal patients, will be discussed as an example together with the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B20. **Other treatments:** Trastuzumab: 15–35% of the patients with breast cancer will show an overexpression of the oncogene c-erbB-2. Herceptin has been shown in the metastatic setting to increase the survival of patients expressing the oncogene and several trials examining its role in the adjuvant situation has been set up. Results of these trials will only be available in a few years time, but possible public health issues related to this therapy will be discussed.

Conclusions

Adjuvant treatment in early breast cancer is changing from a non-specific, risk-related, non-selective use to a tailored treatment that is adapted to the characteristics of patients and their tumours. In particular, the use of predictive gene expression profiles will help in developing individualised treatments. In order to detect subpopulations that may benefit from specific treatments, we will need very large clinical trials including many thousands of patients.

References

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