Endocrine Therapy – What Else?

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Endocrine therapy was the first targeted therapy in breast cancer. In 1896, George Thomas Beatson reported the successful treatment of three young women who had locally advanced breast cancer by removing the ovaries [1]. Beatson understood that ‘there is some ovarian influence which works the change’. This seminal work founded oophorectomy the treatment of choice for premenopausal women with breast cancer. Elwood Jensen discovered the estrogen receptor as the target for this type of treatment [2]. Approximately three quarters of all invasive breast tumors and at least half of all cancers in premenopausal women are estrogen or progesterone receptor-positive. The natural history of hormone receptor-positive disease differs from that of receptor-negative disease regarding time to recurrence, site of recurrence and overall survival. Most important, however, is the enhanced sensitivity of hormone receptor-positive tumors to endocrine therapy. Hormone receptor expression is only a weak prognosticator. Despite the powerful action of endocrine manipulation on tumor biology endocrine therapy has been more and more displaced by chemotherapy [3]. The evolution of adjuvant therapy especially in younger women is complex and several reasons explain the present attitude towards endocrine therapy. Especially in early trials both, hormone receptor-positive and -negative patients, have been included. Several of the early trials were small and underpowered and led to misleading results. One very important confounding factor is the effect of adjuvant chemotherapy on ovarian function. Therapy induced amenorrhea explains at least in part the beneficial effects of cytotoxic therapy [4]. Indeed, several randomized trials testing chemotherapy versus endocrine therapy did not find a significant difference and if, endocrine therapy was superior. Further analyses indicate that preferentially those women experienced a beneficial effect by chemotherapy who developed therapy induced amenorrhea. However, there remain some incomprehensible aspects of endocrine therapy: In

postmenopausal women aromatase inhibitors have been shown to be superior to anti-estrogen treatment [5]. In premenopausal women the ABCSG-12 trial failed to demonstrate superiority of anastrozole over tamoxifen combined with gosereline [6]. The major difference between the treatment arms was caused by the addition of zoledronic acid. Bisphosphonate treatment not only reduces therapy induced bone loss, but in addition displayed marked anti-tumor efficacy. It was very interesting to note that not only occurrence of bone metastases but also other distant as well as local recurrence of the disease was affected. This was surprising and opens new discussion. Since aromatase inhibitors are known to cause bone loss and osteoporosis a high proportion of patients should be given bisphosphonates as additional treatment. This might affect outcome and an unequal distribution of this therapy in a randomized trial might cause an important bias.

The question is: Could the difference between tamoxifen and aromatase inhibitors be caused at least partly by a higher frequency of bisphosphonate treatment in osteopenic/osteoporotic patients? Re-analysis of clinical trials such as the ATAC-trial is crucial to examine distribution of bisphosphonate therapy in both treatment arms. One very important matter concerning both, premenopausal and postmenopausal women, is the identification of those patients that respond most probably to endocrine therapy. Breast cancer is a heterogeneous disease, this becomes apparent in hormone receptor-positive carcinoma. Estrogen and progesterone receptor determination is a valid tool for therapy selection. However, from the treatment of advanced disease it becomes obvious that about half of the patients with receptor positive tumors will not respond to endocrine manipulations. Over the past several years studies using gene expression profiling have demonstrated that distinct genetic patterns allow to identify at least two subtypes of hormone receptor-positive disease,

often referred to as luminal A and B. These results led to the development of gene assays like Oncotype DX or Mammaprint which promise the prediction of recurrence probability and allow a better selection of appropriate adjuvant therapy. However, at least in the European countries this type of patient selection has not obtained wide support. Further validation seems to be necessary before general application can be advised. Classical prognostic factors may be sufficient to select breast cancer patients for solely endocrine therapy. One important prerequisite for effective therapy is of course adherence to selected treatment. However, available evidence suggests that patient adherence especially to oral anticancer agents is quite variable, with reported adherence rates ranging from 20 to 100% [7]. As a result of a prospective analysis performed by Bonadonna and Valagussa it became evident that breast cancer patients who received 85% or less of their prescribed adjuvant chemotherapy had shorter relapse free and total survival than those who received a

more complete treatment [8]. Patients who received less than 65% of planned therapy showed markedly inferior disease-free survival. Thus, evaluation of patient's compliance is warranted. Although patients prefer tablets to injections, oral therapy is more frequently associated with non-adherence. A study by Partridge et al. revealed that nearly one quarter of patients missed to take tamoxifen on more than one fifth of days during the first year of treatment [9]. Furthermore compliance decreased to 50% in the fourth year of therapy. These numbers might be even worse in the case of aromatase inhibitors, since they are known to provoke more side effects with reduced quality of life. Especially bone and joint pain might result in non-adherence to the life saving treatment. Since endocrine therapy has been demonstrated to prevent recurrences in hormone responsive breast cancer patients to a similar extent as cytotoxic therapy it is necessary to develop strategies which will increase adherence of cancer patients to oral medications.

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