Modern Therapeutic Concepts of *Early* Breast Cancer

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This issue of BREAST CARE covers modern therapeutic concepts of *early* breast cancer – after all, all of us in the clinical and research breast oncology community work hard in order to ensure progress for our patients in this curable stage of the disease – following the principle ‘the optimal way to cure is to avoid and prevent relapse and generalization’. Definitely, we are making progress: At least in central Europe, of all women diagnosed with breast cancer in the year 2014, more than 75% will die from something else (which for the breast oncologist is the – somewhat artificial – definition of cure from breast cancer).

With 3 out of 4 women diagnosed with early breast cancer cured, the concern of overtreatment clearly is an issue [1]. In fact, we have reached this point by *adding* therapies to previous standards, as well as implementing new therapies (with new side effects). Understandably we hesitate to abandon anything of our great progress – and in some areas of early breast cancer treatment the combination therapy overkill has gotten out of hand. An example: is it really justified to treat a patient with a 6 mm primary hormone-receptor positive and HER-2/neu overexpressing tumor with 6–8 cycles of adjuvant cytotoxic chemotherapy, followed by 1 year of anti-HER2 treatment, combined with at least 5 years of endocrine therapy? Without any adjuvant treatment and despite the partly unfavorable biological characteristics, this particular patient would look at an approximate 90% probability of 10-year disease free survival, and despite the fact that with all the above-mentioned treatments we might be significantly pushing this up to above 95% (which means halving her risk of relapse), the question remains: *is it worth the price?* The price is paid by the patient with all the tolerability issues she has to handle, with numerous visits to hospitals and offices, with concomitant investigations and the ever-involved fears – but a price must also be paid by society, which has to bear the cost for all these treatments. I am not in any way advocating therapeutic nihilism, but we have so far largely failed to find an evidence-based guidance for really balanced assessments, and several interesting tools that have been proposed [2] never really made it into routine clinical practice. Moreover, I have the sneaking suspicion that we often fail to completely inform our patients about the realistic numerical benefits of the treat-

ments we propose; probably because of concerns they might not follow our advice.

The basis for accurate decision-making, however, is accurate knowledge: this is the purpose of focusing this issue of BREAST CARE on modern concepts of early breast cancer care. In their excellent review article on axillary surgery, Toralf Reimer and his colleagues concisely narrate the tale of a real revolution in breast surgery [3]: despite all the nice talk about personalized medicine concepts, no other field of clinical routine was even remotely as dramatically revolutionized as axillary surgery. What more than a hundred years ago started as a ground-breaking concept [4] that enabled modern surgical oncology by being more ‘radical’ (and thus understanding the ‘regional’ nature of the malignant disease), has recently been reduced in a step-wise manner: less surgery to the breast was followed by less surgery to the axilla and may even be pushed further to no surgery whatsoever for some patients [5]. Despite some severe concerns about methodology and trials details, axillary radiotherapy is also considered an alternative by some [6].

Michael Knauer and his colleagues from the ABCSG [7] provide an excellent overview on current concepts and recent trial results with respect to another clinically extremely relevant question of adjuvant endocrine therapy: how long to treat? While the introduction of tamoxifen therapy has increased survival rates still more profoundly than any other later innovation, we have constantly increased treatment durations: From 3 months to 6 months to 1 year to 2 years to 5 years, and data from the last decade suggest that 10 years may be most beneficial [8], at least for some patients. Is this trend necessitated by the nature of hormone-receptor positive breast cancer, or does it merely mirror our inability to identify those individuals who really need prolonged treatment durations (which unfortunately inevitably means prolonged exposition to therapy-related side effects)? Recently, several multigenomic assays have been described, proposing that we could identify who would be at persisting risk of late metastasis and who would not [9, 10], which provides hope that we can leave the policy of treating all for the benefit of a few.

Besides surgery and drug therapy, radiotherapy is a cornerstone of modern treatment of early breast cancer. Also in this

field, great innovations have been achieved, but inevitably also leave us with the challenge to resolve the conundrum of overtreatment. While many of us have tried in randomized controlled trials to spare some patients with perceived low risk of local relapse after breast conservation the side effects and logistic burden of adjuvant radiotherapy, we so far have largely failed to accurately identify a subgroup for which no benefits could be recorded [11]. Sergio Maluta and his colleagues describe an alternative approach: rather than whole breast radiotherapy or no radiotherapy for women with a favorable risk profile, they apply intraoperative radiotherapy (IORT) [12]. This may at least minimize the logistical burden of irradiation. The concept of accelerated partial breast irradiation (APBI) definitely warrants further investigation – other than delivering only the boost intraoperatively, APBI

conceptually minimizes patient burden more consequently. It remains to be seen, however, how long-term local control results as well as objective long-term aesthetic assessments finally will play out, also in terms of the health economy perspective. For that reason, the authors correctly conclude that this approach currently should only be used in the framework of clinical trials.

While we all like to praise the era of individualized breast cancer therapy, we have to humbly acknowledge that – outside the field of HER2-overexpressing breast cancer – major progresses are, at least for the time being, usually achieved with breakthrough innovations for unselected patient populations. Clinical practice will, for now, have to remain based on guidelines and consensus recommendations [13] – the future has yet to arrive.

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