Targeted Therapy of Breast Cancer

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In 1896, G. Beatson and colleagues published the first cases of young women in which they observed a response on surgical measures now interpreted as surgical ovarian ablation. At that time, the authors were not aware that they had addressed the most common target in breast cancer, now known as the estrogen receptor. It took more than half a century thereafter until the understanding of tumor biology of breast cancer became the most important basis for individualized therapy. Today, we realize that there is no such single entity as ‘breast cancer’, but that we face a basket of malignant diseases with a common origin in the mammary gland with a variety of tumor biological features which we only start to understand.

While we cannot exactly estimate the magnitude of the survival impact of understanding tumor biology, the exploration of predictive factors, and the treatment of cell surface expression markers as well as signal transduction targets, there will be little controversy on its contribution for improved survival of breast cancer patients. Many factors, such as early detection, less invasive and more effective locoregional treatment, and improved systemic treatment will all be important contributors to the decreasing mortality rates in breast cancer, which are observed since the beginning of this century. Based on the understanding of breast cancer as a primarily systemic disease, systemic treatment might offer the highest impact to influence the cure rates of our breast cancer patients.

For decades, the hormone receptor status was the only available predictive factor for targeted treatment. The knowledge about the detection of hormone receptor expression and addressing this target in approximately two thirds of our patients by selective estrogen receptor modulators, aromatase inhibitors, ovarian function suppression, and estrogen down-regulators leads to a mortality benefit of approximately 10/100 patients and has already saved the life of hundreds of thousands of women. By combining novel agents that influence intracellular signal transduction, the efficacy of endocrine has been enhanced even more. The most important modes of action comprise m-TOR inhibition, CDK4/6 inhibition, and PI3K inhibition; these will be summarized in this issue of ONCOLOGY RESEARCH AND TREATMENT. The combination of conventional endocrine therapy and these novel agents will further

improve the efficacy of antihormonal therapy and may overcome endocrine treatment resistance at least temporarily in many patients. However, the impressive array of possible treatment combinations and sequences warrants an enormous amount of further research to identify optimal treatment algorithms. Further research will also have to focus on the exploration and establishment of predictive factors, which are urgently needed to identify patients who will benefit most from these agents and to avoid overtreatment and the unnecessary costs for patients who will not derive benefit from the new options.

For 40 years, HER2-targeted treatment has now been the mainstay of the treatment of patients with HER2-neu overexpressing tumors. The addition of HER2-targeted treatment not only provides improvement of progression-free survival in patients with advanced disease, but also leads to improved overall survival, something that is rarely achieved in metastatic solid malignancies. While patients with HER2-overexpressing tumors initially faced decreased overall survival before the era of targeted treatment compared to patients with HER2-non-overexpressing tumors, they now encounter the reversed situation with a superior prognosis compared to these patients. The low toxicity of most HER2-targeted agents favors the combination with conventional treatment. Further improvements include novel agents, combining monoclonal antibodies and cytostatic agents as conjugates, leading to improved efficacy and decreased toxicity. Dual targeted treatment strategies have led to significantly improved overall survival in advanced breast cancer and will be assessed with prospective data in early breast cancer soon.

Individualized treatment should not only comprise diversification of treatment agents based on tumor biology, but should also take into account different patient conditions, especially the age of patients and age related factors. Improved long-term survival of young patients and the demography driven rise in the incidence of breast cancer in elderly patients will lead to the clinical necessity to further differentiate our treatment behaviors. In this issue of ONCOLOGY RESEARCH AND TREATMENT, we will dedicate one article particularly to this topic of emerging importance.

Exploring the deepening understanding of tumor biology in breast cancer, its phenotypic heterogeneity and its relevance to conventional and novel targeted treatment options, as well as patient related factors in early and advanced breast cancer is the

scope of this issue. On behalf of the editorial board, I hope that this issue will stimulate the readers' insight into the fascinating world of breast cancer treatment.