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Novel therapeutic approaches: immunotherapy

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Immune approaches to the therapy of ovarian cancer have evolved substantially over the past years, from treating patients with nonspecific immune stimulants to a focus on the use of tumorassociated antigens (TAAs) as specific targets for immunotherapy. Tumor-specific immunological interventions can be categorized into passive immunotherapy with antibodies targeted directly to tumor cells or active immune therapy via vaccination with tumor cells, tumor cell lysates, peptides, carbohydrates, gene constructs encoding proteins, or anti-Id antibodies that mimic TAAs, a given antigen. In the nearest past the use of monoclonal antibodies with different targets eg. CA125, Epcam, EGF, VEGF showed a major impact for these approaches in future concepts. This review provides an overview of recent clinical trials using various concepts of immunotherapy for the treatment of ovarian cancer.
Possible reasons for limited clinical success as well as further progress to improve efficacy of current immune intervention strategies, e.g. by vaccines targeting a broader range of tumor-derived antigenic structures or activating diverse host immune functions, will be discussed.

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Novel therapeutic approaches: molecular targeted therapy

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Progress in the management of ovarian cancer has been slow over the past 10 years despite the considerable chemosensitivity of the disease. In most cases, drug resistance supervenes after repeated courses of treatment, and novel molecular targeted drugs are therefore being explored using a range of approaches. One of the most promising targets is VEGF which is an angiogenic growth factor of particular biological importance in ovarian cancer. As a single agent, the anti-VEGF monoclonal antibody, Avastin, has demonstrated antitumour efficacy in advanced disease. Large-scale randomized trials, combining paclitaxel/carboplatin with Avastin, both during and in consolidation treatment following chemotherapy, are planned for first-line studies.
Increasing attention is being paid to the treatment of relapsed disease, and planned trials in this context include combinations of carboplatin with the demethylating agent, decitabine, which has the ability to reverse resistance in experimental models. Other molecular targets include the ErbB family of receptors, and clinical trials will involve both the small molecule inhibitors and the monoclonal antibody, Omnitarg. Interestingly, the one response to the EGFR inhibitor Gefitinib in a Phase II trial in ovarian cancer was linked to a mutation in the catalytic domain of the receptor, in a manner similar to that found in non-small cell lung cancer [1].
Anti-angiogenic agents are also receiving considerable attention in the context of relapsed disease; in addition to Avastin a range of small molecule kinase inhibitors show promise in this respect, and will shortly enter randomized trials.
Other pathway-specific molecules may well find a role in ovarian cancer, particularly those such as HSP90 inhibitors which affect the P13 kinase-AKT pathways, which may play a central role in drug resistance. In this context, combinations with taxanes may be particularly appropriate.
Ultimately, real progress may be expected by a better understanding of the key signalling aberrations causing drug resistance; novel molecular targeted agents – probably in conjunction with conventional chemotherapy – may then be utilized in patients most likely to benefit [2].

References

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Scientific Symposium

Molecular dissection of breast tumour: will it impact on clinical practice?

118 Abstract not received

119 Abstract not received

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Does genomic signature help with the choice of chemotherapy regimens?

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Microarray technologies have had dramatic implications for cancer research and hold great promise for improved diagnosis, prediction of outcome as well as treatment strategies. The ability to measure gene expression across thousands of genes simultaneously in small tissue samples has revealed that there is great molecular heterogeneity among tumors with multidimensional variation in their pattern of expression, even within tumors from the same anatomical site and with similar histo-morphological characteristics. This has so far led to two important discoveries, for breast cancer as well as for other malignancies: First, the classification of tumors into distinct groups based on specific gene profiles, and second, that the biological relevance of such tumor taxonomy is accompanied with significant prognostic impact. This has first and foremost been relevant for prediction of overall- and disease-free survival, but much research is now focusing on how to use genomic signatures to predict treatment response and aid in the choice of therapy. The discovery of several subtypes of breast cancer that are characterized by specific gene expression patterns give clues about affected signaling pathways and cell type origin. These in turn are great sources for predictive markers and therapy targets that are specific for each molecular subtype of tumors. While supervised analyses have revealed gene signatures associated with response to defined regimens, none of these had detection sensitivities sufficient for clinical implementation. Extensive validation and testing of performance of the various gene signatures remains before such models should be used in clinical practice. A deep understanding of the underlying biological processes and mechanisms controlling tumor behavior is needed to be able to predict drug sensitivity.

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Prediction of response to chemo- and endocrine-therapy

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Prediction of response to drug therapy has long been sought as a prerequisite to tailor therapeutic intervention to the specific characteristics of the tumor and the individual needs of the patients. Pioneering work based on patterns of tumor gene expression in breast cancer have been conducted in recent years. This work led to the definition of breast tumor “signatures” of gene expression that have prognostic and to some extent predictive value. A critical aspect in the development of tools which would enable prediction is their standardization and widest possible applicability. Such a feature is not prominent for techniques, such as DNA microarrays, which generally are dependent on the availability of fresh tumor samples. However, high throughput RT-PCR technology can be used to analyze the fragmented RNA that is extracted from formalin-fixed paraffin embedded (FFPE) tumor specimens. The advantage of such an approach is dual: it allows for analyses of large clinical trials in which patients were already followed for years; and can in principle be applicable to any case of breast cancer for which a FFPE sample is available. At the National Cancer Institute of Milan we investigated patients undergoing preoperative (neoadjuvant) chemotherapy for locally advanced breast cancer to identify gene expression markers that predicted the likelihood of chemotherapy response. At the same time, we tested whether the likelihood of chemotherapy response was correlated with the 21 gene Recurrence Score assay that has been validated by the NSABP as a predictor of recurrence risk (Paik et al., N Engl J Med 2004; 2817–26). The latter predictor provides an estimate of the individual likelihood or relapse in women with early breast cancer who received tamoxifen adjuvant systemic therapy. The patients with locally advanced breast cancer analyzed in the present study were treated with paclitaxel and doxorubicin followed by paclitaxel weekly monotherapy prior to surgery. RNA was extracted from the formalin-fixed paraffin-embedded core biopsies that were obtained prior to treatment. The expression of 384 genes selected from available literature