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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

120 INVITED

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

and databases was quantified using RT-PCR. Given that pathologically confirmed complete eradication of the tumor in the breast (pCR) is a robust independent predictor of efficacy, the correlation of gene expression with pathologic complete response (pCR) was determined.
Overall, 89 of 95 patients were evaluable (mean age 49.9 years, mean clinical tumor size 6.4 cm). Eleven patients (12%) had a pCR. A total of 86 genes correlated with pCR ($p < 0.05$, unadjusted). Increased likelihood of pCR was associated with higher expression of proliferation-related genes (e.g., CDC20, E2F1, MYBL2, TOPO2A) and immune-related genes (e.g., MCP1, CD68, CTSB, CD18, ILT-2, CD3z, FasL, HLA.DPB1), and lower expression of estrogen receptor-related genes (e.g., ER, PR, SCUBE2, and GATA3). To further explore whether the findings bore a general vale, we tested the performance of the identified genes in predicting pCR in an independent group of neoadjuvant chemotherapy patients, for whom gene expression was measured using DNA microarrays. In 82 patients who had been treated with neoadjuvant paclitaxel and doxorubicin at the MD Anderson Cancer Center, DNA microarray data were available for 79 of the 86 genes identified as predictors in the RT-PCR study. These genes showed response discriminating value in the microarray data. More specifically, in univariate analysis 24 genes correlated with pCR with $p < 0.05$ (false discovery = 4 genes) and a total of 32 genes showed correlation with $p < 0.1$ (false discovery = 8 genes). Finally, the when the Recurrence Score assay was investigated in the 89 patients form the Milan study, a significant positive association with the likelihood of pCR ($p = 0.005$) was found. In other words, patients who are at greatest risk of recurrence according to the Recurrence Score are also those more likely to benefit from chemotherapy. In conclusion, quantitative expression of ER and other ER-related genes, proliferation genes, and immune-related genes are strong predictors of pCR in women with locally advanced breast cancer undergoing therapy with regimens containing anthracyclines and paclitaxel. Additional analyses are ongoing to refine the findings we have described by comparing the pattern of expression before therapy and after therapy for those who did not achieve a pCR. This will eventually lead to the definition of a predictor for testing in independent validation studies.

Scientific Symposium
Local treatment of prostate cancer

122 Abstract not received

123 INVITED

Intensity modulated radiotherapy (IMRT) for prostate cancer: an update

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Technological advances made over the past two decades have enhanced the precision and improved the outcome of external beam radiotherapy of prostate cancer. 3D-CRT, and in particular IMRT, have greatly facilitated the ability to deliver higher tumor doses while concomitantly decreasing toxicity. The results of the MSKCC dose-escalation study in prostate cancer have confirmed this notion. Of the 1684 patients enrolled so far in this study, 304 patients underwent prostate biopsies 3.5 years after 3D-CRT/IMRT. Biopsy proven local control was dose dependent, increasing from a 44% local cure with 64 Gy to 77% with 75.6 Gy and 88% with 81 Gy. Long-term results of 81 Gy IMRT are now available for 171 patients, followed for a median of 6.3 years (range: 1–7.75 years) after treatment. The 5-year actuarial risk for grade 2 rectal bleeding was 4% and for grade 3 it was 0.5%. For urinary toxicity the risk was 9.5% for grade 2 and 0.5% for grade 3. No toxicities developed later than 62 months from completion of therapy. The incidence of erectile dysfunction post radiation was 44% among patients potent prior to treatment. The 6-year PSA relapse free survival was 91% ($n = 65$), 73% ($n = 71$) and 64% ($n = 35$) for patients with favorable, intermediate and unfavorable risk disease, respectively ($p = 0.008$). The post-treatment biopsy findings at 3 years correlated with long-term PSA relapse free survival, confirming that this biochemical marker indicates a local tumor cure. PSA relapse with a positive post-treatment biopsy in patients with favorable or intermediate risk disease was associated with an increased rate of distant metastases. In contrast, distant metastases in unfavorable risk patients did not correlate with biopsy findings, suggesting such patients may have micrometastatic disease at the time of initial treatment. These data indicate that high-dose (81 Gy) IMRT in localized prostate cancer is safe in that it involves an extremely low risk of complications, and is mandatory for achieving the maximal likelihood of local tumor cure.

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Image guided radiotherapy

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To account for geometrical uncertainties and variations during radiotherapy, safety margins are routinely applied. In many cases, these safety margins overlap organs at risk thereby limiting dose escalation. The aim of image-guided radiotherapy is to improve the geometrical accuracy by imaging the tumor and critical structures on the treatment machine just prior to irradiation. The NKI has collaborated in the development of a kilovoltage cone beam CT guided linear accelerator. A prototype system has been in use for about 2 years, and two commercially released systems have just been taken into clinical use. The system extends the regular accelerator with an extra kV tube and aSi imager. Scan times (with concurrent reconstruction in the background) on the commercial system range from 35 s (small field of view, head and neck) to 120 s (large field of view, prostate). Preliminary results show that the image quality of the commercial system is similar to that of the prototype system, i.e., prostate localization is well possible with about 4 cGy imaging dose. For other anatomical locations less dose is required (we use 1 cGy for head and neck and 2 cGy for lung, 4D scanning). The availability of high quality tomographic images and automatic image analysis (registration) on the treatment machine has quickly led to the introduction of many new clinical applications in our institute. The most exciting ones are high precision hypofractionated treatments of brain metastases and solitary long tumors with on-line tumor position corrections. Patient localization with 1 mm accuracy (for bony anatomy) is easily achieved with the current equipment. Pre- and post-treatment scans demonstrate negligible patient motion (bony anatomy), i.e., about 0.5 mm SD, both for brain and bladder cancer patients. Another advanced application that is now in routine clinical use is adaptive radiotherapy (ART) of prostate cancer, where we determine and adapt the plan to the average prostate position based on cone beam scans made during the first week of treatment. The availability of cone beam CT on the linear accelerator makes this technique very efficient, since the patient does not need extra appointments for CT scans. It is also more accurate, since problem duplicating the setup of the treatment machine on the CT scanner do not occur. An important tool that we have implemented for these protocols is automatic registration of a selected region of soft tissue anatomy. This tool is used for automatic localization of the prostate, as well as for lung tumor setup based on 4D (respiration correlated) cone beam CT. However, for all image-guided protocols, the residual uncertainties need to be taken into account, and the safe level of margin reduction evaluated. For instance our prostate ART protocol allows a reduction of the margin from 10 to 7 mm. In conclusion, cone beam CT guided radiotherapy is now very much a clinical reality. The involved physicians and therapists are very enthusiastic.

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Brachytherapy instead of surgery?

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Introduction: Defining an optimal tailored treatment in localized prostate cancer is not an easy task in lack of prospective randomized trials. The only way to find out which group of patients profit from a certain treatment method is analysing comparable long-term outcome data.
Material and Methods: *Initial PSA* (iPSA), *Gleason score* (GS) and *tumour stage* has all independent and significant influence on treatment results. Many authors have shown, that in patients treated with conventional external beam therapy with iPSA > 10ng/mL the PSA failure was over 50%. This cohort of patients has also a higher probability in both, in extra capsular invasion as well as in the treatment failure rate.
Brachytherapy as monotherapy in localized low- and intermediate risk prostate cancers results in experienced hands to similar long term survival rates as it can be achieved by radical prostatectomy performed in centres of excellence, however, quality of possible toxicities caused by both treatments is different. Operated high-risk group cancers need frequently postoperative radiotherapy complementary to radical prostatectomy to reach best possible cure. The possible addition of toxicities caused by radical prostatectomy and full dose radiotherapy result in higher risk of loosing quality of life for the patient, therefore, dose escalation radiotherapy (combined EBRT+Brachytherapy) seems to be more advantageous in this group. In case of dose escalation radiotherapy (>80–90 Gy_{BED}) complementary systemic treatment (androgen deprivation) could be advantageous in cases with high risk of systemic disease (iPSA > 30 ng/ml).