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Timing of hormonal therapy in prostate cancer

D. Melloni, M. Pavone-Macaluso. *Institute of Urology, University of Palermo, Italy*

The optimum timing for starting hormonal treatment in prostate cancer is still a matter of discussion.

Low-grade Clinically Confined Prostate Cancer: There is a growing experience in the deferred treatment of patients with low grade clinically localized prostate cancer indicating a high rate of local progression, a moderate rate of distant progression and low mortality due to tumour up to 10 years observation.

Prior To Radical Prostatectomy: Hormonal treatment prior to radical prostatectomy is even more controversial. The few randomized trials currently in progress will eventually show whether this approach can lead to improved survival.

Positive lymphnodes at or after radical prostatectomy: Should endocrine therapy be started immediately at the time of diagnosis, or should treatment be deferred until evidence is gained of progression? The ongoing FORTC Trail 30864, still in progress, will hopefully answer this question.

Advances Stages of Prostate Cancer: There are sufficient medical and ethical reasons to advise and employ early endocrine therapy in patients with metastatic prostate cancer.

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Is micrometastasis the target of preference for monoclonal antibody therapy?

G. Schlimok. *Medical Clinic II, Zentralklinikum Augsburg, Germany*

Purpose: A review of the clinical trials of antibody-based cancer therapies reveals that this approach can, in rare cases, induce complete remissions in individual cancers. Since these trials have usually involved patients with large tumor masses, tumor cell inaccessibility in probably a major reason for the prevailing failures. Minimal residual disease, the stage when tumor cells are few and dispersed, should therefore be a more promising target for the therapeutic antibodies.

Results: In breast cancer patients infusion of monoclonal Lewis Y antibody as well as monoclonal antibody 17-1A, directed against an epithelial adhesion molecule, led to a reduction of disseminated tumor cells in bone marrow. These observations were supported by a prospective randomized adjuvant trial, using monoclonal antibody 17-1A in patients with resected Dukes'C colorectal carcinoma, which resulted in increased survival and prolonged recurrence-free intervals.

Conclusion: Thus, in addition to strategies designed to produce more effective human-derived reagents, efforts need to be concentrated on directing passive antibody therapy towards the appropriate target.

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Antibody therapy of lympoid malignancies: Experience with CD52 (CAMPATH-1) antibodies

M.J.S. Dyer. *Academic Haematology, Academic Haematology and Cytogenetics, Institute of Cancer Research-Royal Marsden Hospital, UK*

Although monoclonal antibodies (MAbs) have the specificity to deliver targeted therapy, several barriers may preclude their routine use in lymphoid malignancy. Notably, only certain target antigens expressed on specific cell types are permissive for cell lysis or induce cell death by other methods: eg CD20 MAbs induce apoptosis in some malignant B-cells. CD52 MAbs were originally isolated for their ability to lyse lymphocytes with human complement. Subsequent work showed that rat and human CD52 MAbs also able to elicit antibody-dependent cellular cytotoxicity consistently depleted lymphocytes from blood, marrow and spleen whereas lymph nodes and extra-nodal masses were usually resistant: since activity of CD52 MAbs depends on the activation of cellular effectors, resistance may reflect their absence in these sites. Clinically useful activity of CD52 MAbs has therefore been demonstrated primarily in the chronic lymphoid leukemias. T-cell prolymphocytic leukemia (T-PLL) is remarkably sensitive to CD52 MAbs with most patients entering durable remissions. The biological basis of this sensitivity is not known. Secondly, patients with fludarabine-resistant B-CLL may usefully respond: in particular, clearance of the blood and marrow has allowed harvesting of uncontaminated stem cells. A similar approach of "*in vivo* purging" may be of value in patients with non-Hodgkin lymphoma undergoing high-dose chemotherapy.

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Monoclonal antibodies in combination with growth factors and chemotherapeutics

H. Mellstedt. *Department of Experimental Oncology, Uppsala University and Academic Hospital, Sweden*

Introduction: Unconjugated monoclonal antibodies (MAb) targeted to tumor cells mediate tumor lysis by activating various immune functions and/or induce apoptosis. Immune functions include antibody dependent cellular cytotoxicity (ADCC), complement dependent cytolysis (CDC) and induction of a tumor specific humoral and cellular idiotypic network response. Thus, it may be plausible to assume that augmentation of immunological effector mechanisms may increase the antitumor effect of MAb.

Results: In various clinical trials GM-CSF and IL-2 have been added to the MAb with the aim to augment ADCC as well as the idiotypic network response. α-interferon has been given to enhance unspecific killer functions and increase the expression of tumor antigens. Cytostatics have been administered also with the goal to decrease tumor volume. Combinations have mainly been given in colorectal carcinoma, melanoma, NHL and ovarian carcinoma. Improved effects might be seen during certain conditions but also impaired clinical results as well as decreased immune effector functions. The effects might be dose-schedule dependent. A survey of clinical studies with emphasis on clinical results and immune effector functions will be presented.

Conclusion: Improvement of MAb therapy might be possible by adding other biologicals and/or cytostatics. However, the dose-effect relation seems to be complex. Careful clinical and immunological analyses have to be done in man to be able to optimize the concept.

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Is there a future for clinical use of bispecific monoclonal antibodies?

S.O. Warnaar. *Centocor B.V., The Netherlands*

A review will be presented on the current state of therapies with bispecific monoclonal antibodies (biMabs).

BiMabs are very effective *in vitro* in mediating destruction of tumor cells. Either T-cells or F_c receptor bearing effector cells can be recruited.

In animal studies both localized (in traperitoneal) and systemic tumors can be effectively treated with biMabs and effector cells.

In patients some encouraging results – including complete responses – have been obtained in advanced glioma as well as in ovarian cancer by local application of the biMab. Despite these results no real breakthrough has been reported.

Issues are: the difficulties of purifying biMabs, the need for supplying activated effector cells, toxicity related to release of cytokines and the immune response against biMabs of murine origin.

Various approaches to overcome these issues will be discussed.

Conclusion: BiMabs have a future in combating advanced disease, however considerable hurdles still remain.

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Antibody-targeted activation of cellular immunity

L. Weiner. *Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA*

Altering the tumor microenvironment by cytokine therapy and the induction of cytotoxicity by cellular components of the innate and adaptive immune system have long been goals of cancer therapy. Relatively rare, but intriguing clinical responses have been observed in clinical trials of these strategies. One obstacle to the successful implementation of these strategies is the absence of selective targeting of cellular cytotoxicity to tumor sites; this obstacle is compounded by the limitations of cell trafficking to tumor sites. Multifunctional antibody binding site-based proteins can provide cellular activators with tumor-targeting properties, and have been extensively evaluated in preclinical models and clinical trials. Conventional antibodies with appropriate Fc domains can mediate antibody-dependent cellular cytotoxicity (ADCC), but this property has dubious clinical relevance to cancer therapy. Bispecific antibodies (Bsab) targeting tumor antigens and the defined cellular trigger molecule FcγRIII expressed by human natural killer cells exhibit improved anti-tumor properties in preclinical models, and one such Bsab has completed Phase I evaluation at our center. We also have investigated the novel immunoconjugate PNU 21-4565, a recombinant protein composed of an antibody Fab fragment and the bacterial super-