



Report

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Athens, Greece 15 – 17 November 2007

Introduction

Approximately 150 delegates met in Athens for this meeting which was intended to review the state of the art in immunotherapy of cancer and to provide an update on the immunological principles underlying this therapeutic approach. This was a truly multidisciplinary meeting with a mixture of basic scientists and clinicians actively involved in the field of immunotherapy. The program was organized such that there was adequate time for discussion and indeed some of the discussion sessions were extremely thought provoking.

The meeting opened with a keynote lecture by Professor John Wagstaff, UK, who gave a historical review of the field of immunotherapy. The initial phase of this treatment approach was with non-specific immune stimulators. He pointed out that William Coley, an American surgeon working at the Memorial Hospital in New York, first treated cancer patients with a heat killed suspension of bacteria (Coley's toxin) at the end of the 19th century. There are many publications relating to this vaccine and there is undoubted evidence that some

cancer patients achieved remissions with this approach. Indeed, Coley's fluid was still in the formulary of the USA National Cancer Institute until the mid 1960s. During the 1950s, 60s and 70s a number of (anti-)microbial agents were tested for their anti-cancer effects. These included Bacillus Calmette and Guerin (BCG), *Cryptosporidium parvum* and levamisole. The latter agent combined with 5-fluorouracil enjoyed a period of favor as an adjuvant treatment for colon cancer. BCG is still in use today as a therapy for superficial transitional cell bladder cancer.

Cytokine treatment

The next era, which has lasted until today, is that of cytokines produced by recombinant DNA technology. Such agents include the interferons, interleukin-2 and the hematopoietic growth factors.

Interleukin-2 produces complete responses (CR) in 7-8% of renal cancer patients. These CR patients have an 85% chance of being alive at 10 years and are probably cured. More recently it has been shown that by selecting patients whose tumors over-express carbonic

anhydrase IX the 5-year survival rate is 40%. High-dose bolus IL-2 is therefore still a viable treatment strategy for this group of patients.

The interferons still have a role in the management of a number of rarer cancers such as carcinoid, chronic myeloid leukemia and renal cancers amongst others, although their use is likely to wane with the introduction of the new targeted therapies.

Granulocyte-macrophage colony stimulating factor (GM-CSF) has become an important adjuvant for many of the new vaccine strategies.

Monoclonal antibodies and vaccination

In the modern era of immunotherapy, vaccine development and the use of monoclonal antibodies have begun to take center stage. These developments were reviewed during this meeting and the most recent developments are summarized in the next sections.

Karin de Visser from the Netherlands Cancer Institute illustrated the fact that the infiltration of immune cells within the tumor stroma is not always beneficial to the host. Infiltration with macrophages and B lymphocytes with antibody deposition correlates strongly with angiogenesis and is essential for tumor progression. Professor Griffioen, the Netherlands, also pointed out that during angiogenesis there is down-regulation of the adhesion molecules on endothelial cells and this limits the ability of immune effector cells to enter the tumor stroma and attack cancer cells. This down-regulation can be reversed by the use of chemotherapeutic agents and anti-angiogenic agents, suggesting that the combination of these approaches may be a valid way of enhancing (adoptive) immunotherapy.

A number of monoclonal antibodies (MOABs) are now licensed for the treatment of cancer. Although many of these target growth factor receptors, a number of them are also able to activate complement-dependent and antibody-dependent cellular cytotoxicity. Jan van de Winkel, the Netherlands, and Carl Borrebaek, Sweden, described important advances in the development of MOABs, and it is now possible to make fully human MOABs which will undoubtedly increase the clinician's armamentarium against cancer.

Several speakers addressed the biology and utility of Natural Killer (NK) cells in cancer immunotherapy. Professor Wagstaff showed data from a Japanese study which suggested that high levels of NK activity in normal people protects them against the development of cancer. Rolf Kiessling, Sweden, discussed the role that super-oxide radicals have in mediating immune suppression. He showed that NK cells are particularly susceptible to apoptosis induced by reactive oxygen species (ROS). Also the administration of high-dose vitamin E (antagonizing ROS activity) enhances NK and T helper 1 activity in patients with colorectal cancer. A randomized trial giving histamine plus IL-2 in leukemia patients in remission increased leukemia-free survival from 20% to 36% at 60 months from randomization.

There is clear evidence that inhibiting the ROS pathway can lead to significant therapeutic effects which are mediated at least in part by immune modulation.

Hans-Gustaf Ljunggren, Sweden, also demonstrated that optimal activation of NK cells was dependent on the appropriate expression of receptors on target cells and that one mechanism of immune escape might be the down-regulation of these receptors.

Vaccine development for patients with advanced cancer has been an active area of clinical research over the last 15 years. The current perception is that this approach has not lead to significant clinical advances. John Wagstaff, Angus Dalglish, UK, and Rik Scheper, the Netherlands, emphasized that clinical trials had produced significant relapse-free and overall survivals in patients with colon and renal cancers. Unfortunately, these patient-individualized approaches are not attractive to the pharmaceutical industry and there have also been regulatory hurdles because licensing authorities cannot decide whether these vaccines are 'medicines' or 'procedures' in the same way that stem cell transplants are. Both Pierre Coulie, Belgium, and Pedro Romero, Switzerland, demonstrated that it is possible to measure T cell responses against peptide vaccines albeit at lower levels than are seen with viral vaccines. Clinical responses to these vaccines are sporadic and have not yet proven clinically meaningful. In an excellent keynote lecture Cornelis Melief, the Netherlands, clearly demonstrated that long peptides were to be preferred for vaccines over short ones and made the statement "Don't ever use short peptides for clinical trials except for tolerance induction in autoimmune disease!!" He pointed out that vaccines directed against the E6 and E7 epitopes of the human papillomavirus (HPV) are now licensed for the prevention of cervical cancer. In a phase I trial of a long peptide in patients with advanced cervical cancer one patient achieved a CR lasting more than 3 years. Five others had stable disease lasting between 1.5 and 3+ years. HPV16-specific T cell responses were seen in 18/18 patients with vulval *in situ* neoplasia (VIN) and there was complete clearance of VIN grade 3 lesions in 5/20 patients and clearance of HPV 16 infection in 4/20 patients. This is an extremely promising vaccine. Several speakers addressed the issue of the role of regulatory T cells in mediating anergy to vaccines. Approaches designed to remove these T cells using chemotherapy or antibodies as well as vaccinating against FOXP3 T cells (Gilboa) are being actively pursued in both the laboratory and the clinic.

Allogenic stem cell transplantation

The role of allogeneic stem cell transplantation was discussed by Shimon Slavin, Israel. He demonstrated that this can be a powerful tool to induce remissions in patients with solid tumors. He made a plea for applying this therapy in earlier stages of the disease.

Conclusion

During this meeting many aspects of tumor immunology and immunotherapy were addressed. It was clear that this approach to cancer treatment still shows considerable promise and increases in knowledge combined with technological advances might lead to important clinical advances within the next 5 to 10 years.