New perspectives in cancer immunotherapy and immunomonitoring

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Cancer Immunotherapy and Immunomonitoring, Kiev, Ukraine, 18–21 May 2009

The first international conference ‘Cancer Immunotherapy and Immunomonitoring (CITIM)’ took place in Kiev, Ukraine, and was organized by the international (Chair – Michael Shurin, University of Pittsburgh Medical Center, PA, USA) and local (Chair – Dmitry Bazyka, Research Center for Radiation Medicine, Kiev, Ukraine) organizing committees. The main aims were to discuss the mechanisms of immune regulation in the tumor microenvironment, the efficacy of anticancer immunotherapeutic modalities, the results of clinical trials and the methods of patient immunomonitoring. This report provides a short overview of novel concepts, strategies and clinical achievements in this quickly developing field of oncology. Almost 200 participants from 26 countries of Europe, Asia, Africa and North America were attracted by the scientific program that consisted of presentations from 45 international experts. Good memories remain, not only from the lively discussions of eight plenary sessions, two specially selected presentations and 50 posters, but also from the beauty of ancient Kiev and the social evenings in the downtown with local food and drinks.

Tumor progression & immunity

The conference was opened with the keynote lecture of Robert Wiltout (Center for Cancer Research, NCI, MD, USA), who discussed experimental and clinical aspects of kidney cancer immunotherapy based on cytokine combinations. Application of interleukin (IL)-12 with IL-2 was demonstrated to induce regression of metastasis. Moreover, agonistic anti-CD40 antibodies, together with IL-2 or IL-12 plus IL-18, could mediate anti-tumor effects and overcome an immunosuppressive tumor microenvironment. Wolf-Hervé Fridman (University Pierre et Marie Curie, Paris, France) focused on the role of *in situ* immune responses in human cancer. High infiltration of colon and lung tumors with Th1 and CD8 T cells, as well as the presence of chemokines attracting these cells,

was demonstrated to correlate with patient survival. Ron Apte (Ben-Gurion University, Beer-Sheva, Israel) presented a broad overview of the involvement of IL-1 in tumor progression, and its immunotherapeutic implications. Whereas IL-1 β promotes tumor-mediated angiogenesis and immunosuppression, IL-1 α induces effective anti-tumor immunity. The important issues of molecular mechanisms of radiation-induced leukemia, and lung cancer associated with a strong immunosuppression, were analyzed by Dmitry Bazyka.

Regulatory & effector mechanisms in the tumor microenvironment

Of special interest was the ‘Breakthroughs in CITIM’ presentation by Francesco Marincola (NIH, Bethesda, MD, USA), which included the concept of an immunological constant of tumor rejection that includes the coordinate activation of interferon-stimulated genes and immune effector function. An interesting approach for the quantitative noninvasive monitoring of dendritic cells (DC) involved superparamagnetic iron oxide particles associated with tumor antigen being captured by magnetic resonance imaging, and was reported by Hyam Levitsky (Johns Hopkins University, MD, USA). New strategies used by tumors for their progression and immune escape, in particular, upregulation of toll-like receptors (TLR)-7 and -8 or Fc γ receptors (Fc γ R) on the cell surface, were discussed by Catherine Sautes-Fridman (University Pierre et Marie Curie). Angel Pogdador (Ben-Gurion University) presented a broad overview of methods of cancer cell recognition by natural killer (NK) cells, which are regulated by a variety of activating and inhibitory receptors on the NK cell surface. Volodymyr Bebesko (Research Center for Radiation Medicine) pointed out a role of distinct HLA molecules in the predisposition of a population exposed to irradiation for the development of hematological malignancies. Thomas Sayers (NCI, MD,

USA) proposed an original strategy of sensitizing tumor cells to TRAIL- or FasL-mediated apoptosis that could be combined with different types of immunotherapy.

Tumor microenvironment & cancer immunotherapy

The presentations in this session focused on the use of immune regulation in the tumor environment to increase the efficiency of cancer immunotherapy. Federico Garrido (University Hospital, Granada, Spain) emphasized a key role of the unaltered HLA class I expression on tumor cells for the development of T-cell-mediated anti-tumor responses and clinical effects after cancer immunotherapy. The importance of the tumor immune environment for systemic anticancer responses in a colon carcinoma animal model was also stressed by Luca Vannucci (Institute of Microbiology, Prague, Czech Republic). Paul Neeson (Peter MacCallum Cancer Centre, Melbourne, Australia) characterized the effector memory status of gene-modified human CD8 T cells and provided evidence of their persistence after adoptive transfer into patients. Another approach of sensitizing tumor cells to apoptosis induced by glucocorticoids using the protein kinase inhibitor staurosporine was reported by Eitan Yefenof (Hebrew University, Jerusalem, Israel). The immunogenicity of tumor cells, and thereby the anti-tumor effects of cancer immunotherapies, can be augmented by the implementation of the phosphatidylserine ligand annexin A5, as reported by Udo Gaipf (University Hospital, Erlangen, Germany). The pivotal significance of IL-1 β secreted by tumors and surrounding host cells for tumor progression and angiogenesis was stressed in the presentation by Elena Voronov (Ben-Gurion University). An important issue of overcoming the tumor endothelial barrier by normalization of the tumor vasculature for successful cancer vaccination or adoptive T-cell immunotherapy was addressed in another 'Breakthroughs in CITIM' presentation by Gunther Haemmerling (German Cancer Research Center, Heidelberg, Germany).

Preclinical models of cancer immunotherapy

The first two presentations made by Viktor Umansky (German Cancer Research Center) and Arthur Hurwitz (NCI) were focused on transgenic mouse models of malignant melanoma and prostate cancer, respectively.

In contrast with conventional transplantation models, melanoma and prostate cancer developing in transgenic mice closely resemble the clinical situation, and are of critical importance for the study of tumor–host interactions and the design of novel immunotherapies. Using a mouse model of skin cancer, Galina Shurin (University of Pittsburgh, PA, USA) presented a promising strategy of noninvasive topical immunotherapy based on 'labeling' of tumors with phosphatidylserine, an 'eat-me' signal. Valentin Shichkin (International University Ukraine, Kiev, Ukraine) presented a mouse model of brain tumors treated with the adoptive transfer of tumor-specific T cells combined with DNA vaccination. A transgenic mouse melanoma model was also used by Alexandra Sevko (Research Center for Radiation Medicine), who reported a synergism of low-dose cyclophosphamide therapy and peptide immunization in the increase in anti-tumor immune responses.

Cancer immunotherapy: lessons & perspectives

Michael Papamichail (Saint Savas Hospital, Athens, Greece) presented a broad overview of the modern strategies of cancer vaccination and adoptive cellular immunotherapy, delineating basic aspects of each modality and possibilities to improve their therapeutic efficacy. A comprehensive analysis of clinical trials using multiple peptide vaccination of melanoma and prostate carcinoma patients was presented by Licia Rivoltini (Istituto Nazionale Tumori, Milan, Italy), who stressed the high efficacy of this treatment for patients with early stages of disease. Next, two speakers, Gurkamal Chatta (University of Pittsburgh, PA, USA) and Oleg Eremin (Lincolnshire Hospital, Lincoln, UK), presented data from DC vaccination of patients with prostate cancer and with different advanced malignancies, respectively. The enhancement of tumor-specific T-cell reactions and clinical responses in these patients were discussed. Coming back to mouse models, Lea Eisenbach (Weizmann Institute, Rehovot, Israel) analyzed the reasons behind the relatively low clinical responses in patients demonstrating increased frequency of tumor-specific T cells, including tumor-induced immune escape and immunosuppression. Noah Isakov (Ben-Gurion University) focused on the pivotal role of over-expressed protein kinase C-interacting cousin of thioredoxin (PICOT) in T-cell proliferation in Hodgkin's lymphoma patients.

Regulatory cells & cytokines

This session started with a presentation by Ronald Gress (NCI), who reported on the restoration of T-cell homeostasis after administration of IL-7 into tumor-bearing mice and cancer patients treated with chemotherapeutic drugs. Another important target for cancer immunotherapy, transforming growth factor (TGF)- β , which is associated with higher pathological grade, metastasis and poor survival of cancer patients, was presented by John Morris (NCI). Dmitry Kazansky (Cancer Research Center, Moscow, Russia) analyzed a new subset of neutrophil-like antigen-presenting cells involved in the allogeneic tumor cell recognition by CD8 T cells. Molecular links between immunoregulatory and cancer-associated genes and the regulation of protein–protein interactions with microRNAs were addressed in the presentation by Vadim Fraifeld (Ben-Gurion University). A detailed analysis of the correlation between the amount of regulatory T cells and the severity of graft-versus-host disease was presented by Ilya Korsunsky (Institute of Rheumatology, Moscow, Russia). Anatolii Chumak (Research Center for Radiation Medicine) reported on the involvement of hepatitis C virus infection in the development of hematological malignancies.

New approaches in cancer immunotherapy

This session included presentations discussing interesting new strategies of cancer immunotherapy. Claude Leclerc (Institut Pasteur, Paris, France) proposed a therapy based on the tumor antigen vaccination, TLR ligand CpG and cyclophosphamide, which can induce eradication of large transplanted tumors in 90% of treated mice. Michael Shurin (University of Pittsburgh) presented an application of low, noncytotoxic doses of chemotherapeutic drugs in tumor-bearing mice that stimulate DC activity and could be combined with DC vaccination for successful anti-tumor therapy. To treat multiple myeloma, Qing Yi (MD Anderson Cancer Center, TX, USA) proposed the application of immunization with: peptides derived from the tumor-specific protein Dickkopf-1; vaccination with heat shock proteins combined with CpG and anti-IL-10 antibodies; and monoclonal antibodies against β 2-microglobulin. A type I glycoprotein, CD150, overexpressed in B-cell hematological malignancies was presented in the presentation by Svetlana Sidorenko (Institute of Experimental Pathology, Oncology and Radiobiology, Kiev, Ukraine) as a potential target molecule for

cancer immunotherapy. Natalia Aptsiauri (University Hospital) suggested that the adenoviral-mediated recovery of altered HLA class I expression on tumor cells in combination with vaccination or T-cell transfer may improve the clinical outcome of cancer immunotherapy.

Cancer biomarkers & immunomonitoring

The last session covered different aspects of biomarkers and immunological monitoring of clinical trials. Enzyme-linked immunosorbent spot (ELISPOT) and some other immunoassays, such as Fluorospot, intracellular cytokine staining and fluorescence-activated cell sorting-based killing analysis, were comprehensively discussed in the talks of Claire Horlock (Anthony Nolan Research Institute, London, UK), Paul Lehmann (Cellular Technology Ltd, OH, USA), Bartek Zuber (Mabtech, Nacka Strand, Sweden) and Anatoli Malyguine (NCI). It was stressed that in addition to traditional IFN- γ , other ELISPOT assays were developed to detect T cells producing granzyme B, IL-2, IL-4, IL-13, IL-17 and perforin. Jon Sherlock (Applied Biosystems, CA, USA) reported on the multiplexed TaqMan®-based microRNA profiling strategy that allows such profiling from cancer stem cells that are supposed to be chemoresistant and possess a high metastatic potential. Alina Romanenko (Institute of Urology, Kiev, Ukraine) presented immunohistological detection of ubiquitin and related proteins as markers for urinary bladder carcinogenesis.

Conclusion

This conference was the first in Eastern Europe to focus on the issue of immune regulation in the tumor environment, cancer immunotherapy and immunomonitoring of clinical trials. The immune system is critically involved in the control of tumor progression. We have learned how to manipulate the immune system to generate a tumor-specific immune response. Although immunological treatment protocols have not yet delivered substantial clinical benefits, the results of recent studies suggest that we are on the edge of a real breakthrough in cancer immunotherapy. The CITIM conference demonstrated that by supporting open communication between scientists and clinicians, and sharing ideas and plans, we could accelerate the progress in this area and eventually save the lives of cancer patients.

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