oncology PRO
Educational Portal for Oncologists

ESMO Symposium on Immuno-Oncology 2013: Advances in cancer immunotherapy; from vaccines to antibodies and cell therapies

15-16 November 2013

Geneva, Switzerland

Summary

The increase in knowledge about the way the immune system functions is leading to exciting new therapeutic possibilities for cancer patients. This symposium provided cancer specialists with a comprehensive overview of the interaction between the immune system and cancer. The major themes covered the role of the immune system in cancer, clinical studies in immuno-oncology across tumour types, cancer immunotherapy implications for clinical practice, promising therapeutic strategies and integration with other therapies/combination approaches.

Introduction

The Symposium was designed for medical oncologists, basic and clinical researchers with an interest in immunology aspects in cancer, and all medical professionals keen to learn more on advances in cancer immunotherapy and their implications for clinical practice.

The Symposium objectives were to provide an essential update to oncology professionals on reinitiated interest in the role of the immune system in cancer, present the latest achievements in immuno-oncology research across range of malignant diseases, elaborate on different issues relevant for clinical practice and to provide a forum for discussion on perspectives of promising therapeutic strategies, including combination with other treatment modalities.

Cancer immunotherapy refers to a number of approaches intended to activate the immune system to induce objective responses and disease stabilisation. Renal cell cancer (RCC) and melanoma are natural targets for such approaches, because both tumour types are frequently infiltrated with CD8+ lymphocytes, and occasionally undergo spontaneous regressions. By contrast, non-small cell lung cancer (NSCLC) has been considered to be insensitive to immunological approaches because immunotherapy with cancer vaccines had not demonstrated clinical benefit and spontaneous regressions had not been observed. Now, clinical data suggest that this is not the case; objective responses in NSCLC have been reported in trials involving agents that block immune checkpoint molecules. Indeed, the largest interventional clinical trial ever initiated for NSCLC, involving over 2,200 patients, is testing a vaccine directed against the protein MAGE-A3, a cancer-associated protein that belongs to a class of molecules known as cancer-testis antigens, expressed only in tumours and in germ cells. What melanoma, lung and RCC cancers have in common are new and exciting data that show a significant rate of objective clinical response to antibodies that block immune checkpoints, a treatment that has rapidly been advanced into randomised phase III clinical trials.

Over 300 registered participants conveyed in Geneva, Switzerland with approximately 75% of attendees coming from Europe, 10% from Asia, 7% from North America and other attendees were from Middle East, Central and South America, Africa and Australia. Top ten countries by number of attendees were Switzerland, UK, France, USA, Belgium, India, Germany, Italy, Portugal and Czech Republic. The European Society for Medical Oncology (ESMO) as an organiser of this event delivered a substantial number of travel grants to enhance attendance of young medical oncologist and all of those interested to keep abreast with scientific advances.

In report from this Symposium, a review of the basic immunology underlying an anti-tumour immune response is first discussed and then results in tumour types reviewed, with a focus on both cancer vaccines and immune checkpoints inhibitors. It is beyond the scope of the report to provide all different aspects discussed during the Symposium; it provides highlights from some of the sessions.

Basics in cancer immunology and immunotherapy

Although a comprehensive review of the basic immunology aspects underlying an anti-tumour immune response is beyond the scope of this report, a few introductory points are worth to be mentioned.

Cancer vaccines are used in approaches that seek to raise a specific T-cell or B-cell response against cancer. When a vaccine is injected into the skin, components of the vaccine known as pathogen-associated molecular patterns activate resting dendritic cells (DC) and programme them to migrate to a local lymph node. Thus, a vaccine generally includes components intended to activate DCs and the precise agents used vary widely between different vaccines. Another common term for these activating components is ‘adjuvant’, as they ‘add’ immunogenicity to the protein or peptide components of a vaccine. The other key component of a vaccine is the target protein or peptide that is expected to be overexpressed in tumours compared with normal tissue. The choice of vaccine antigen(s) is somewhat empiric and, similar to adjuvant selection, varies widely between cancer vaccines. Once a resting DC has been loaded with antigen, activated, and has migrated to a lymph node, it then displays fragments of proteins in the form of small peptides. Cellular recognition of antigens is complex; peptides are not presented alone, but instead are bound within a genetically diverse set of host molecules collectively encoded by a set of genes within the major histocompatibility complex (MHC). Specific receptors on CD4+ and CD8+ T cells recognise a structure composed of both MHC molecules and a specific peptide. Simple recognition is

insufficient for full T-cell activation; T cells must also receive additional activation signals provided by functionally mature DCs to proliferate and acquire effector function. In the case of CD8+ T cells, the desired effector function is the ability to lyse target cells that express the same MHC–peptide complex that served to activate them, that is, their target antigen. Once fully activated, CD8+ T cells leave the lymph node, and traffic widely through the body in search of their targets.

Unfortunately, most tumours have evolved multiple mechanisms to evade immune-mediated destruction. One of these mechanisms involves cell-surface expression of one or more of a series of molecules that effectively limit T-cell proliferation and killing capacity. Collectively, such molecules are referred to as immune checkpoints, perhaps the best known of which is cytotoxic T-lymphocyte antigen-4 (CTLA-4). Early preclinical studies using transplantable murine colon carcinoma and fibrosarcoma lines showed that blocking CTLA-4 permits anti-tumour T cells to acquire effector function, a finding that has recently been borne out in randomised phase III studies in patients with metastatic melanoma. In large, randomised phase III trials, blocking CTLA-4 with the monoclonal antibody ipilimumab resulted in a significant survival benefit. Long-term follow-up from the trials showed that some of treated patients were lived even 10 years after enrolment. The clinical trials of anti-CTLA-4 (including the pivotal phase III trials) were associated with an approximate 20% incidence of grade 3 and 4 immune-related adverse events (IRAEs), including colitis and dermatitis.

A second immune checkpoint, programmed death-1 (PD-1), has garnered significant interest as the blockade of PD-1 with a single-agent associated with objective responses in melanoma, RCC, and perhaps somewhat surprisingly, lung cancer. Toxicity rates are difficult to compare given that PD-1 blocking antibodies have only recently entered phase III development. Nonetheless, the rate of grade 3 and 4 adverse events seems to be lower with PD-1 blockade than with CTLA-4 blockade, possibly because the PD-1/PD-ligand (PD-L1) pathway acts more peripherally than the CTLA-4/B7-1 pathway, which may operate in the lymph nodes. In contrast to cancer vaccines, objective tumour regressions and long-term complete responses, have been routinely observed with both PD-1 and CTLA-4 blockade, driving enthusiasm for ongoing phase III and combination trials. At the current time, it remains unclear why cancer vaccines rarely generate objective tumour shrinkage, but accumulating clinical data suggest that current vaccines may be unable to circumvent effectively the multiple immunosuppressive mechanisms operative in the tumour microenvironment.

Vaccines versus checkpoint inhibitors

In clinical practice, achieving objective anti-tumour responses through vaccination is quite rare, although at least one phase III trial has documented improved overall survival with the vaccine sipuleucel-T in prostate cancer resulting in subsequent drug approval. Cancer vaccines remain valid research approaches in lung cancer, RCC and melanoma, with at least six randomised phase III trials in various stages of accrual and completion. It is worth

mentioning that one of these trials, the MAGRIT trial of a MAGE-A3 vaccine for NSCLC is the largest interventional trial ever conducted in that disease, reflecting the interest in bringing a lung cancer vaccine to patients.

In very sharp contrast, immune checkpoint blockade with CTLA-4, PD-1 and PD-L1 blocking antibodies has demonstrated clear evidence of objective responses, driving renewed enthusiasm for cancer immunotherapy in multiple cancer types. This reinvigoration is perhaps most prominent in the case of NSCLC, which was previously thought to be a tumour type insensitive to immunotherapy. Indeed, two agents blocking PD-1 have rapidly moved from phase I to phase III trials in multiple tumour types, setting the stage for a series of results that are eagerly awaited over the next several years. Notably, several of these trials seek to combine conventional therapy with immune checkpoint blockade.

In her lecture on checkpoint inhibitors anti-PD1/anti-PD-L1 versus anti-CTLA-4, Caroline Robert of the Institute Gustave Roussy, Villejuif, France said that benefit/risk ratio is in favour of PD1/PDL-1 blockade over CTLA-4 blockade. Combination of these two approaches is currently evaluated. Relevance of PD-L1 expression is explored. However, she opened a lot of questions that are unaddressed at the moment, e.g. optimal treatment regimen, long term adverse events, when to stop the treatment, maintenance treatment, potential of combination with other strategies, as well as a problem of resistance mechanisms.

Monitoring of immune response

In his lecture on monitoring of immune response during immunotherapy, Michael Kalos of the Penn Institute for Immunology, Perelman School of Medicine, University of Pennsylvania, USA said that successful development and implementation of biomarker studies requires quality-supporting infrastructure, assays that enable hypothesis generating insights and infrastructure to support integrated meta-analysis of data. The application of quality-supported biomarker platforms and studies that enable more comprehensive, hypothesis generating evaluation of patient samples offers the opportunity for functional and mechanistic insights into T cell immunotherapies.

Response evaluation in cancer immunotherapy

In his lecture on response evaluation in immunotherapy, Jedd Wolchok of the Memorial Sloan Kettering Cancer Center, New York, USA discussed on unique kinetics of response in patients treated with ipilimumab. In particular, some patients treated with ipilimumab have been shown to have unique time courses for their anti-tumour responses. In addition, patients might have prolonged stable disease followed by regression, while some patients have an initial response with slow induction of a complete response. Others have new lesions, meaning progressive disease, but then have either prolonged stability or a subsequent response.

In his presentation, he showed examples of four patterns of response to ipilimumab therapy observed: two conventional with response in baseline lesions and “stable disease”

with slow, steady decline in total tumour volume. Two novel patterns observed are namely response after initial increase in total tumour volume and response in index plus new lesions at or after the appearance of new lesions.

Furthermore, he summarised that checkpoint blockade is an effective treatment with durable responses. The mechanistic biology of immunotherapy calls out for revised response criteria to accurately assess outcomes with imaging correlates. Intense study of both predictive and pharmacodynamic biomarkers of response and toxicity will allow for more intelligent patient selection and novel target discovery.

Immunotherapy in lung cancer

In the lecture about vaccination approaches in lung cancer, Johan Vansteenkiste of the Respiratory Oncology Unit, Department of Pulmonology, University Hospital Leuven, Belgium said that immunotherapies were traditionally considered more appropriate for low burden disease, e.g. early and locally advanced NSCLC. In recent cancer vaccination studies, better defined antigens and adjuvants were used. Generally low toxicity observed in these studies could define a unique treatment opportunity. Recent data from phase III study with L-BLP-25 vaccine show 10 month improvement in median overall survival after concurrent chemo-radiotherapy for stage III NSCLC. Data of largest phase III therapeutic study in NSCLC on postoperative MAGE-A3 vaccine are awaited.

In the presentation on clinical activity of anti-PD1 in NSCLC, Scott Antonia of the Moffitt Cancer Center, Tampa, USA elaborated that with follow-up extended to 1-2 years in heavily pretreated patients, nivolumab produces durable responses, demonstrates an encouraging survival profile and can be used in an outpatient setting with manageable safety profile. Tumour response can continue following discontinuation of therapy. It is unclear yet whether combination with chemotherapy produces added benefit. PD-L1 as a biomarker needs additional study.

In addition, he discussed on how to optimise immunotherapy. Tumours evolve to develop multiple potential mechanisms whereby tumours evade rejection by the immune system. It is needed to continue to discover targets and develop agents. “Driver” versus multiple mechanisms should be considered. Personalised medicine considers biomarker driven selection of appropriate therapeutic strategy for individual patients. Combinations with vaccines, tumour-infiltrating lymphocytes (TILs), chimeric antigen receptor (CAR)-modified T cells should be considered.

Immunotherapy in melanoma

In his lecture on immuno-oncology clinical studies across tumour types and melanoma as a proof of concept, Olivier Michielin, of the Department of Medical Oncology, Ludwig Center, Swiss Institute of Bioinformatics, Lausanne, Switzerland divided strategies into active and passive and then each of them classified under those with a narrow or large antigenic specificity. Active strategies with large antigenic specificity that demonstrated high response rate and long-term benefit are CTLA-4 blockade, PD-1 blockade and CTLA-4 plus PD-1 blockade. Adoptive transfer using TILs is a passive strategy with large antigenic specificity and showed the same benefits. However, adoptive transfer using engineered T cells (TCRs, CARs) is a passive strategy with narrow antigenic specificity that demonstrated only high response rate. Peptide-based vaccines belong to are active strategy with narrow antigenic specificity but none of the above mentioned efficacy endpoint were observed.

Immunotherapy in prostate cancer

In his lecture on immunotherapy for prostate cancer and lessons from translational research, Winald Gerritsen of the Radboud University Medical Center, Department of Medical Oncology, Nijmegen, the Netherlands said that in clinical practice, achieving objective anti-tumour responses through vaccination is quite rare, although a phase III trial has documented improved overall survival with the vaccine sipuleucel-T in prostate cancer resulting in subsequent drug approval for patients with castration-resistant metastatic prostate cancer and when chemotherapy is not yet considered appropriate.

Immunotherapy in RCC

Cytokine therapy with interferon-alpha or interleukin-2 (IL-2) has been shown to induce objective responses, and interferon-alpha appears to have a modest impact on survival in selected patients. Interferon-alpha has approximately a 15% objective response rate in appropriately selected individuals. In general, these patients have non-bulky pulmonary and/or soft tissue metastases with excellent performance score of zero or one, according to the ECOG rating scale, and the patients show no weight loss. The interferon-alpha doses used in studies reporting good response rates have been in an intermediate range. A Cochrane analysis of six randomised trials indicated average improvement in survival of 2.6 months.

High-dose IL-2 produces a similar overall response rate to interferon-alpha, but approximately 5% of patients had durable complete remissions. IL-2 has never been shown in a randomised, controlled trial to result in longer survival. The optimum dose of IL-2 is unknown. High-dose therapy appears to be associated with higher response rates but with more toxic effects. Low-dose inpatient regimens have activity against RCC with fewer toxic effects, especially hypotension, but have not been shown to be superior to placebo or any alternative regimen with regard to survival or quality of life.

CTLA-4 blockade has been evaluated in patients with metastatic RCC; a phase II trial with ipilimumab showed partial responses, grade 3 or 4 IRAEs were observed in 33% of

patients, potentially a higher rate than that observed in melanoma patients. Interestingly, a clear association between immune-related toxicity and responses was observed in that trial as well. At this time, single-agent CTLA-4 blockade is not under study in RCC, most likely owing to competition from the relative plethora of targeted agents, both approved and in clinical trials, according to Martin Gore of the Royal Marsden Hospital, London, UK who provided an overview of immune-oncology clinical studies in RCC.

Indication of clinical activity for PD-1 blockade in RCC was supported by data from the trial in which the objective response rate was 30–35%, with an additional 10% of patients showing prolonged stable disease. On the basis of the activity seen in phase I trials, three phase I and II studies of nivolumab in RCC have been initiated, and a phase III trial is now open to accrual. A second, perhaps more-interesting trial incorporates carefully collected pretreatment and post-treatment biopsies in an effort to define biomarkers predictive of response. A phase I study combining PD-1 blockade with the tyrosine kinase inhibitors pazopanib or sunitinib was initiated. Most importantly from a clinical standpoint is a potentially pivotal, randomised phase III study. This trial will randomly assign 820 previously treated RCC patients in a 1:1 ratio to receive either nivolumab or to standard second-line therapy with the mTOR inhibitor everolimus. The primary end point of the study is overall survival.

The leading vaccine approach in RCC focuses on targeting multiple carefully selected antigens with a less complex adjuvant. This approach identified a set of nine tumour-associated peptides, which were incorporated into a vaccine using granulocyte-macrophage colony stimulating factor (GM-CSF) as an adjuvant. GM-CSF is a strong inducer of DC migration, but perhaps less robust than several of the toll-like receptor (TLR) agonists in terms of inducing DC activation. A randomised phase III trial has been initiated with IMA901 added to first-line sunitinib in patients with metastatic RCC.

Autologous cancer vaccines, manufactured from lysate or whole cells from tumours from individual patients, have been tested in RCC. As expected, such approaches are complicated by the variability and complexity in generating a vaccine from variable amounts of tissue from patients. A phase III trial of AGS-003 is currently in progress in patients with metastatic high-risk RCC to receive either sunitinib alone or one cycle of sunitinb followed by AGS-003 co-administered along with sunitinib. The primary end point of the study is progression-free survival.

An additional method to generate a cancer vaccine is to incorporate the target antigen into a viral backbone. Poxviruses are particularly well-suited for such approaches. A randomised phase II trial of TG4010 was carried out with RCC patients treated with cytokine therapy or cytokine therapy plus TG4010. Although the vaccine was well-tolerated, no significant overall survival differences were noted between the two treatment arms.

Immunotherapy in breast cancer

In his lecture about a model of breast cancer and immunotherapy implication for clinical practice, Giuseppe Curigliano of the Breast Cancer Program Division of Early Drug Development, Istituto Europeo di Oncologia, Milano, Italy, presented results of two early

phase studies, namely phase I open-label dose-escalation vaccine trial of dHER2 protein with AS15 adjuvant in HER2-overexpressing patients with high-risk breast cancer and open-label phase I/II trial of the safety and efficacy of the dHER2 recombinant protein combined with immunological adjuvant AS15 in patients with HER2-positive metastatic breast cancer.

He discussed about challenges for therapeutic vaccination, especially endogenous immunity (features leading to disease eradication versus tolerance), stromal elements influencing local immunity, challenges to achieve sterile immunity versus resetting equilibrium and rescuing a failed host response.

Therapeutic vaccination in breast cancer represents opportunity to drive setting of clinical trials according to the expression of the antigens in cancer subtype, selection of patients with no or minimal tumour burden, to perform correlation studies of immunological/clinical response and evaluation of genetic/immunological profile of responders. He emphasised on complexity of cancer, tumour heterogeneity and immune escape and lack of definitive biomarker(s) for assessment of clinical efficacy of cancer immunotherapies. Conventional clinical response criteria do not take into consideration differences between response patterns to cytotoxic agents and immunotherapies. He underlined that academic breast cancer research community desperately need clinical trials with immunotherapy.

Combinations with other therapies

In the lecture on immunotherapy combinations with chemotherapy, Martin Reck of the Department of Thoracic Oncology, German Center for Lung Research (DZL), Lung Clinic, Grosshansdorf, Germany spoke about interaction between immune system and chemotherapy, interaction between immune system and targeted therapies, rationale for combination of chemotherapy and immunotherapy and first encouraging results of combination of check-point inhibition and chemotherapies. He emphasised that validation is needed in randomised trials. He divided his talk on combination data of ipilimumab and chemotherapy in melanoma and lung cancer and combination strategies for anti PD-1 and chemotherapy.

Immunotherapy combinations

In his lecture on immunotherapy combinations, Cornelis Melief of the Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands said that concentrated antigen delivery (DNA, RNA, synthetic long peptide - SLP) with appropriate adjuvants is crucial. Synthetic vaccines allow rational vaccine design. Favoured cancer target antigens are involved in cancer initiation, progression and/or metastasis (example are oncogenic proteins E6 and E7 of high risk HPV). Long peptide vaccines harbouring both CD4 and CD8 T cell epitopes and requiring DC processing are efficient. DNA prime/long peptide boost may be considered. Processing route of SLP appears to differ from that of proteins. Further improvements have been seen by adding pegylated type I interferon or TLR ligands but especially by conjugating TLR ligands to the long peptides. For maximally effective cancer treatment, development of

combination treatment should be considered, such as long peptide vaccination with chemotherapy or irradiation and inhibitors of checkpoint control monoclonal antibodies (CTLA-4 blocker, PD-1, PD-L1 blockers, anti-IL6 (R), anti-IL10 (R), anti-TGFβ (R) and other immunomodulators). Reduced toxicity of the monoclonal antibody treatments may be achieved by local delivery in slow release formulation close to tumour-draining lymph nodes. Adoptive transfer of cancer-specific T cells is best combined with optimal vaccination.

Novel approaches to molecular vaccines

In his lecture on novel approaches to molecular vaccines, Sebastian Kreiter of the TRON-Translational Oncology, Johannes Gutenberg - University Mainz, Germany said that a significant fraction of mutations is immunogenic. Prediction algorithms may be applicable to increase immunogenicity rate beyond 20%. Candidate driver as well as non-driver mutations are applicable as vaccine targets. Mutated CD4 epitopes are of proven anti-tumoural value. Combination of vaccines coding for mutated and non-mutated epitopes can provide anti-tumoural synergy. Neo-epitopic stretches generated by Indel mutations might qualify as particularly attractive vaccine targets. Vaccine format (RNA/peptide) may have an impact on results.

Related information

Click here to access the Symposium webcast page.

Affiliation and disclosure

Dr Svetlana Jezdic, ESMO Head Office.

No conflict of interest to disclose.