BJMO clinic

Belgian Journal of Medical Oncology

Special edition
Immuno-oncology

THE BELGIAN JOURNAL OF MEDICAL ONCOLOGY IS THE OFFICIAL JOURNAL OF THE BELGIAN SOCIETY OF MEDICAL ONCOLOGY (BSMO) AND THE BELGIAN ASSOCIATION FOR CANCER RESEARCH (BACR)

COLOPHON

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Special editions are distributed amongst medical specialists in Belgium, such as oncologists, surgeons and radiotherapists.

PUBLISHER AND EDITORIAL OFFICE
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The content of this special edition of the BJMO was reviewed by the editorial board of the BJMO.

COVER ILLUSTRATION
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ISSN-NUMMER
1784-7141

BJMO immuno-oncology special

INTRODUCTION

DEAR READER

Over the last five years, immune checkpoint inhibitors (ICIs) have drastically altered the outcome of an increasing number of cancer patients with a broad range of cancer types. Currently, single-agent PD-1 or PD-L1 inhibitors are the standard immunotherapy in most cancers. This issue reviews the progress on several fronts, including novel strategies.

In some cancers **combined CTLA-4 and PD-(L)**1 inhibition has been investigated resulting in increased efficacy but also toxicity in melanoma, renal cell carcinoma, and non-small-cell lung cancer.

The treatment for patients with **small cell lung cancer** (SCLC) has long been at a standstill with chemotherapy being the only treatment option for more than three decades. The extremely high mutational burden that is seen in SCLC could theoretically predict for high immune-sensitivity, but the initial results with ICI in SCLC were somewhat disappointing (influenced by robust immune-evasive mechanisms?). Nevertheless, in recent years immunotherapy is also making its mark in this disease setting.

Radiotherapy interacts with the tumor microenvironment and the immune system, which, theoretically, could amount to an in situ vaccination and trigger abscopal responses (i.e. responses in non-irradiated disease). Anecdotal cases have illustrated that this abscopal effect is not only a theoretical paradigm. Recently the combination of radiotherapy with immunotherapy is being validated in a large number of clinical trials. In these studies, new concepts have emerged, including the finding that low doses of radiation to metastatic sites (while the primary site is treated a full dose) might be capable of helping systemic immunotherapy or even lead to responses on itself.

A more novel immunotherapeutic strategy consists of **CAR-T cell therapy** and other forms of **cellar therapies**. After initial success in hematological malignancies, these personalized cellular therapies are also moving ahead in solid tumors. Technological issues primarily related to the personalized nature are currently being tackled, which could lead to more rapid development and a broader applicability of this therapeutic strategy. If these vast investigational efforts prove to be successful, CAR T-cell therapy might well represent the next wave of significant progress in cancer treatment in the coming years.

I wish you a pleasant read.

J. de Grève, MD, PhD
Editor-in-chief

Chimeric antigen receptor T-cells: is the success in haematological malignancies translatable to solid tumours?

T. Feys, MSc, MBA[1]; J. de Grève, MD, PhD[2]

SUMMARY

Chimeric antigen receptor (CAR) T-cell therapy is a new cancer immunotherapy targeting specific cell surface antigens. This type of adoptive cell immunotherapy has been a breakthrough in the treatment of aggressive B-cell lymphoma and B-cell precursor acute lymphoblastic leukaemia (ALL) and is currently being studied in other cancer types, including multiple myeloma and chronic lymphocytic leukaemia. With the unprecedented success of CAR T cells in haematological malignancies, a growing number of (pre)clinical studies are focusing on translating this treatment to solid tumours. However, response rates to CAR T-cell therapy have so far been much less favourable in non-haematologic malignancies, mainly due to a paucity of unique tumour target antigens, limited CAR T-cell trafficking to tumour sites, tumour heterogeneity, antigen loss, the presence of an immune suppressive tumour microenvironment and recognition of normal cells expressing the targeted antigen. A broad range of strategies is currently being explored to overcome these hurdles. For example, TCR-CAR-T hybrids have been developed that can also target intracellular antigens which broadens the potential scope of the CAR-T cell strategy. This article reviews completed and ongoing CAR T-cell trials in solid tumours and discusses the strategies to improve the efficacy of this treatment modality in solid tumours, including accelerated production flows. CAR-T's might very well be the upcoming major advance in cancer treatment.

INTRODUCTION

Exploiting the immune system to attack cancer cells is not a new concept. In fact, the development of allogeneic stem cell transplantation (alloSCT) has first highlighted the potential of T-cells to eliminate cancer cells. In this respect, *Kolb et al.* showed that donor lymphocyte infusions can induce long-lasting remissions in patients with relapsed chronic myeloid leukaemia (CML).[2] In adoptive cell therapy (ACT), immune cells are collected from a patient or a donor after which they are manipulated and/or expanded *ex vivo* and reinfused to the patients.[1] The success of ACT mainly depends on the presence of an adequate amount of effector cells in the patients, which in turn requires precursors with either natural anti-tumour recognition, or engineered T cells to provide this recognition.[1] Researchers have developed several strategies to improve the tumour recognition of adoptively stimulated cells. The two main methods employed are T-cells transduced with an engineered

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Conflict of interest: The selection of the studies discussed in this article is the sole responsibility of the author and was not influenced by third parties.

Role of immune checkpoint inhibitors in small cell lung cancer treatment

K. Nackaerts, MD, PhD[1]

In recent years, the potential of several immune checkpoint (ICP) inhibitors in small cell lung cancer (SCLC) has been increasingly investigated. Despite the fact that in some trials the benefit of the addition of ICP inhibitors was only modest, results of the CheckMate-032 and Keynote-028 and 158 have led to the FDA approval of nivolumab and pembrolizumab as third-line treatment options for patients with extensive disease (ED)-SCLC. More recently, results of IMpower 133 formed the basis for the EMA approval of atezolizumab in combination with chemotherapy as a first-line treatment option for ED-SCLC. In addition, several ongoing first-line trials in ED-SCLC patients will report their results in the near future. Also in limited disease (LD) SCLC patients, several trials are examining the interactive effects of concurrent tumour irradiation with chemo- and immunotherapy. Until now, unfortunately, there are no validated biomarkers to identify those SCLC patients who might derive the best long-term survival benefit from chemo-immunotherapy.

INTRODUCTION

Small cell lung cancer (SCLC) accounts for about 10-15% of all newly diagnosed cases of lung cancer. In Belgium, some 1,300 new SCLC cases are diagnosed yearly.[1] SCLC occurs almost exclusively in (*ex*)-smokers and a majority (70%) of these SCLC patients are still diagnosed with an advanced or 'extensive disease (ED)' clinical tumour stage. While treatment modalities for stage IV non-small cell lung cancer (NSCLC) patients have changed tremendously over recent years with the arrival of targeted therapies and immune checkpoint (ICP) inhibition, the first-line treatment with platinum-etoposide chemotherapy for ED-SCLC patients has remained unchanged for almost 30 years. Similarly, also the second-line SCLC therapy with topotecan has been the same for the last 20 years. To date, not a single targeted therapy has been reimbursed for SCLC. In recent years, the potential role of ICP inhibitors in the treatment of SCLC has been increasingly investigated. A high tumour mutation burden (TMB) can be detected in SCLC, like in NSCLC patients. High TMB together with a smoking history are regarded as predictive factors for immunotherapy response in NSCLC patients[2], and thus it was hoped that immunotherapy would also work quite well in SCLC.

IMMUNE CHECKPOINT INHIBITION IN ED-SCLC

Already in 2016, ipilimumab, a cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) inhibitor, was studied in ED-SCLC patients, by adding it to first-line platinum-etoposide chemotherapy in a randomised, phase III study.[3] Unfortunately, the addition of ipilimumab did not result in a significant improvement in the overall survival (OS). Furthermore, compared to chemotherapy, much more patients had to stop their treatment due to immune-mediated side effects,

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Conflict of interest: The author has received personal fees for participating on advisory boards from Roche, AbbVie, Bristol-Myers Squibb; personal fees for giving lectures from Roche; funding to institution (for participation in clinical trials) from Millennium Pharmaceuticals, Inc., AbbVie, Lilly.

Keywords: atezolizumab, durvalumab, immune checkpoint inhibitors, ipilimumab, nivolumab, pembrolizumab, small cell lung cancer, topotecan, tremelimumab.

Radiotherapy in the lung cancer immuno-oncology era

M. Lambrecht, MD, PhD[1]; T. Feys, MSc, MBA[2]

ABSTRACT

Radiotherapy not only allows us to selectively target the tumour, it also interacts with the tumor micro-environment and consequently the host's immune system. Theoretically this can lead to an *in situ* vaccination and trigger so-called abscopal responses, away from the irradiated site. Unfortunately, these are rarely seen the clinic. Over the past years, both preclinical and clinical studies demonstrated synergistic effects of radiation in combination with several types of immunotherapy. However, the optimal dose and fractionation of radiation therapy as well as the optimal combination and sequence of radiotherapy and immunotherapy still needs to be determined.

INTRODUCTION

Nowadays, approximately 50% of all newly diagnosed cancer patients are treated with radiotherapy. For a long time, the efficacy of ionizing radiation has been attributed to its ability to selectively target the tumour in combination with its ability to induce DNA damage, causing direct tumour cell death. More recently, it was recognized that radiation can also contribute to systemic anti-tumour immunity.[1] In fact, radiation therapy has several effects on the immune system. It can lead to immunogenic cell death (ICD), leading to the release of danger associated molecular patterns (DAMPs) and tumour associated antigens (TAA). It can lead to an upregulation of surface molecules on the irradiated cancer cells, making them more visible to T-cell mediated killing. And it can lead to the release cytokines facilitating the recruitement of effector T-cells to the tumour (*Figure 1*).[2-4] These observations are the basis to investigate the full potential of radiotherapy in combination with immunotherapy.

A CLOSE INTERPLAY BETWEEN RADIOTHERAPY AND THE IMMUNE SYSTEM

The effect of ionizing radiation on tumour cells is dependent on dosing and fractionation and causes DNA damage. This damage can be either lethal or sublethal and can initiate a chain of reactions, one of which is ICD.[2] Molecular signals of ICD include the cell surface translocation of calreticulin and the release of DAMPs such as the high-mobility group protein B1 and adenosine triphosphate.[5-7] In contrast, tumour cells that received a sub-lethal dose of radiation undergo phenotypic changes that will increase their recognition and killing by T cells. The enhanced expression of MHC class I molecules, adhesion molecules, stress-induced ligands and death receptors all contribute to this enhanced immune susceptibility. Finally, radiotherapy also causes the release of cytokines, attracting T cells to the tumour site. These radiotherapy induced alteration converts the cancer into an *in situ* vaccine, which creates an

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest. The selection of the studies discussed in this article was not influenced by third parties.

Keywords: radiotherapy, immunotherapy, abscopal, lung cancer, PACIFIC

Immuno-oncology combinations: rationale and clinical implications in melanoma, renal cell carcinoma and lung cancer

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ABSTRACT

Over the past years, immune checkpoint inhibitors have been widely used for the treatment of a broad range of malignancies. Unfortunately, only a proportion of patients derives long-term benefit from these therapeutics. In fact, a majority of patients fails to respond to immune checkpoint inhibition, while others relapse after a certain time. In an attempt to increase the response rate of tumours to these drugs, investigators have looked into the potential of combining different immunotherapeutic agents. Since inhibitors of the immune checkpoints CTLA-4 and PD-(L)1 have different modes of action and given the fact that blocking one of both pathways results in an upregulation of the other, provide a theoretical rationale to combine these agents. This review provides an overview of clinical studies evaluating combinations of CTLA-4 and PD-(L)1 inhibitors in the treatment of melanoma, renal cell carcinoma and non-small-cell lung cancer.

INTRODUCTION

In recent years, an increased understanding of the complex interactions in the tumour micro-environment and the tumour evolution, has led to novel insights in the way tumour cells escape from the immune system. Tumour resident regulatory T-cells (T-regs) highly express the T lymphocyte antigen 4 (CTLA-4), a pivotal checkpoint that negatively regulates effector T-cells. Moreover, tumours also express the programmed cell death ligand 1 (PD-L1), known to trigger T-cell apoptosis and to promote the formation of T-regs upon interaction with the checkpoint programmed cell death protein 1 (PD-1).[1] These checkpoints have become interesting targets for immune checkpoint blockade therapy and by now immune checkpoint inhibitors are widely used for the treatment of a broad range of malignancies. In particular, the clinical success of monoclonal antibodies directed against CTLA-4 and the PD-1/PD-L1 pathway, have revolutionized the treatment of cancer patients.[1] More recently, a number of 'next-generation' immune checkpoint inhibitors (ICI), targeting the lymphocyte-activation gene 3 (LAG-3), the T cell immunoglobulin and mucin domain-3 (TIM-3) and B7-H4, also

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest. The selection of the studies discussed in this article was not influenced by third parties.

Keywords: Immunotherapy, melanoma, nivolumab, ipilimumab, combination, sunitinib, renal cell carcinoma, SCLC, NSCLC, immuno-oncology, checkpoint-inhibitors, durvalumab, tremelimumab, pembrolizumab