BSMO Immunomanager program

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Immunotherapy has become a standard of care for patients with many different advanced solid tumors. However, boosting the immune system can induce immune related side effects, referred to as "immune-related adverse events" (irAEs). Because oncologists are not always familiar with these inflammatory autoimmune syndromes, the BSMO immunotaskforce has launched the immunomanager website which summarizes the treatment options for the most frequent irAEs including endocrine (e.g. hypo- and hyperthyroidism), digestive (e.g. colitis), pneumological (e.g. pneumonitis), dermatological and other types of irAEs. In the near future, the BSMO immunotaskforce plans to review these recommendations with Belgian organ specialists and their associations. We believe that through collaborations between organ specialists and oncologists we will be able to establish better recommendations, resulting in a better outcome for cancer patients who develop an irAE during immunotherapy.

INTRODUCTION

In recent years, immunotherapy has revolutionized the way we treat cancer patients. Metastatic patients with several tumor types can now benefit from long lasting clinical responses with checkpoint inhibition. Furthermore, very promising results have been presented with immunotherapy in the adjuvant setting. In Belgium, checkpoint inhibitors are reimbursed for the treatment of different metastatic cancers and since the first of September, nivolumab is also approved for the adjuvant treatment of melanoma (*Figure 1*). The main goal of immunotherapy is to boost the immune system in order for it to eradicate cancer cells. Side effects are mainly related to the fact that the immune system becomes overactive or recognizes 'self' instead of cancer cells. This results in inflammatory autoimmune-like syndromes with symptoms that are often completely different from the classical side effects seen with chemotherapy or targeted therapy. Because of their different pathophysiology these irAEs require a different treatment, mostly requiring temporary immunosuppressive treatment.

In order to better understand the side effects, oncologists need to understand the pathophysiology of these inflammatory autoimmune syndromes and in a sense become immuno-oncologists. Up to now several types of inflammatory autoimmune syndromes ranging from endocrine to gastrointestinal to neurological pathologies have been reported.[1] Thyroid dysfunction occurs rather often (around 10% in patients treated with anti-PD-1 moncolonal antibodies [mAb]), whereas cardiac side effects are very rare (probably <1%). Because oncologists are not always entirely familiar with autoimmune problems, many symptoms may remain unde

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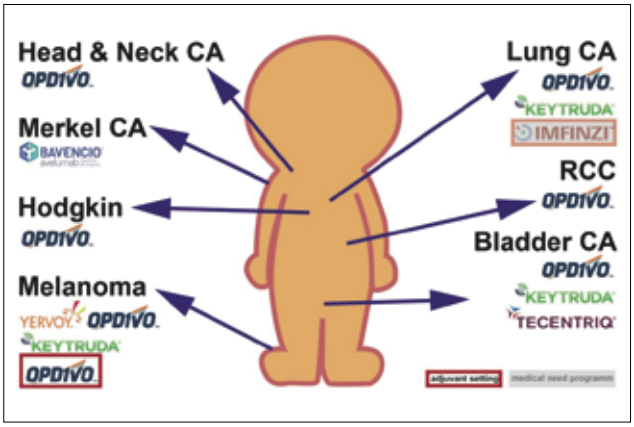

FIGURE 1. Overview of reimbursement of immune checkpoint blockade in Belgium (October 2018). Immune checkpoint blockade is reimbursed in the setting of several types of advanced cancer. Recently reimbursement for the adjuvant setting has been added. There is also one medical need program ongoing and another one for squamous cell carcinoma of the skin is being expected.

tected. This is especially the case when their incidence is low, as is the case for rheumatology, cardiology and neurology related irAEs.[2] Therefore, one of the goals of the BSMO immunotaskforce is to improve the detection and treatment of immune related side effects and ultimately improve the quality of life of patients developing these treatment-related side effects. We are convinced that this initiative will also lead to a better collaboration with organ specialists which will ultimately promote scientific projects in order to better understand, treat and prevent immunotherapy related inflammatory autoimmune-like adverse events.

IMMUNOMANAGER PROVIDES COMPREHENSIVE RECOMMENDATIONS ON THE DIAGNOSTIC ALGORITHM AND TREATMENT FOR THE DIFFERENT TYPES OF irAEs

The first project of the BSMO immunotaskforce consists of the Immunomanager webtool. This is an interactive, online website providing recommendations for different irAEs (*Figure 2*). Up to now, most recommendations have been made based on clinical experience, discussions with organ specialists and the ESMO, SITC, NCCN and ASCO guidelines.[3,4] In a next phase, these recommendations will be validated by the individual organizations of organ specialists. This process was already finalized for the rheumatological side effects (*Figure 3*). To this end, several meetings were set up with the rheumato-onco taskforce (a group of rheumatologists from the Belgian Society for Rheumatology) to discuss the recommendations. The final step in this validation process was the presentation of the recommendations during the national conference of Rheumatology at the end of September 2018. We plan to have meetings with the Belgian organization of neurologists (BNS) very soon and other organ specialties should follow. Interestingly, during these meetings many possible shared projects between oncologists and rheumatologists were discussed which will now lead to a very challenging collaboration across specialties. Additionally, organ specialists now realize that the autoimmune-like pathology we see in cancer patients treated with immune checkpoint inhibitors may resemble some known autoimmune syndromes, such as rheumatoid arthritis, psoriasis, myositis or Guillain

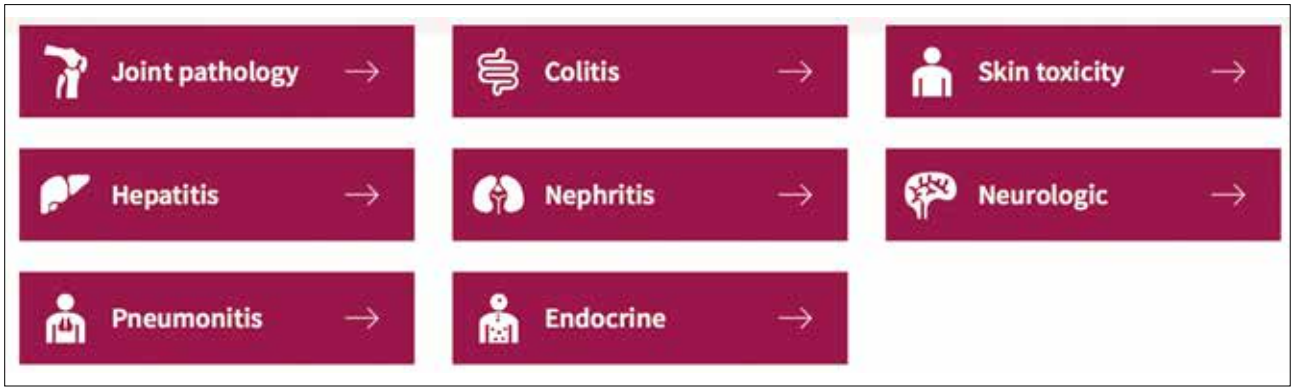

FIGURE 2. Types of immune-related side effects with recommendations in the Immunomanager site of the BSMO (version 1st oct 2018). By clicking on each individual tile, recommendations will pop up for the specific side effects according to their severity (mostly according to CTCAE grading system). Momentarily the following immune related side effects are covered: arthralgia, arthritis, colitis, rash, hepatitis, nephritis, Guillain-Barré (like) syndrome, myasthenia gravis, peripheral neuropathy, pneumonitis, hyper and hypothyroidism and hypophysitis.

Symptom Grade	Moderate or severe pain, limiting instrumental activities of daily living and may disable self care Signs of inflammation such as joint swelling Awaking of pain at night Early morning stiffness (>30min) Multiple joints may be affected Evaluate pain with visual analogue scale
Management escalation pathway	Escalate analgesics and use NSAID (If not contraindicated) Prednisone (10-20mg) to be started ideally after consultation with rheumatologist Withhold ICPI until resolution of symptoms Intra-articular injections only if infection was ruled out (usually done by treating rheumatologist) Consider methotrexate or salazopyrine if steroid refractory or for steroid sparing purposes (experience and not evidence based)
Assessment and investigations	Always do X-ray (consider arthropathy, pre-existing arthropathy, metastasis or baseline evaluation) If possible, try to objectify arthritis (eg by ultrasound or arthrocentesis) Complete rheumatological history regarding differential dia gnosis Examination of all joints Always consider joint aspiration especially when fever or severe inflammation to rule out septic arthritis and crystalarthropathies **Autoimmune panel:** ACPA RF ANA (by indirect immunofluorescence) followed by more specific analysis if posiitive result (according to local practice) ANCA (to be discussed with rheumatologist) Joint biopsy can be done in collaboration with certain centres for scientific purposes

FIGURE 3. Arthritis signifies inflammatory joint disease and is characterized by several typical symptoms. It is very important to make the difference between arthralgia and arthritis as the treatment and outcome are different. Oncologists should collaborate with rheumatologists in order to decide the right treatment and follow up. These recommendations have been setup in collaboration with the rhumato-onco taskforce of the KBVR/SRBR (Koninklijke Belgische Vereniging voor Reumatologie/ Society Royale Belge de Rhumatologie).

Barré syndrome. This offers opportunities to increase the insights in the pathophysiology of these disorders. One of the main problems with some of the described irAEs is their rarity. This significantly limits the experience based learning potential for the individual oncologist. In order to learn on rare side effects, we have to share information and work as a community. Therefore we plan to add an additional window to the immunomanager site with concise descriptions of rare side effects such as vasculitis, fasciitis, meningitis etc. In addition to peer reviewed articles, that often focus on rather exotic side effects, we hope to create a platform for a quick exchange of experiences for all kinds of side effects. Ideally contact details of oncologists who have treated the individual patient could be shared as well.
Last but not least some side effects can be life threatening. This includes myocarditis and some forms of myositis.[5] It is very complicated to inform the patient as those side effects are extremely rare. Nevertheless, reporting on these side effects is highly recommended in order to teach the oncology community as often urgent treatment of a potentially life-threatening irAE could make a difference in outcome.

Now that cancer immunotherapy has become part of our daily routine, many questions arise for the treatment of patients with preexisting immune problems. This ranges from preexisting autoimmune disease to chronic infectious diseases such as chronic Hepatitis C and transplant patients. Up to now, these patients were excluded from clinical trials, resulting in a lack of prospective data. Therefore we would like to invite our colleagues to share these patient cases as well.

CONCLUSIONS

In conclusion, the BSMO immunotaskforce is in the process of launching innovative projects. First of all the immunomanager site offers community available recommendations for the diagnosis and treatment of irAEs. The ultimate aim is to improve the therapeutic index of immunotherapy for all patient groups that could potentially benefit from these agents.

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