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EDITORIAL

Quality of life of cancer patients on the wave of immunotherapy

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Oncologic treatments have evolved as long as the understanding about tumor biology has been elucidated. The number of drugs that are part of the arsenal against cancer reflects the important achievements toward a better clinical outcome. At the same time that several therapeutic options are available and cancer patients are living longer, a new set of challenges needs to be faced by clinicians: rapid recognition and adequate management of treatment-related adverse events (AEs) [1].

Cytotoxic chemotherapy was the backbone of cancer treatment for several decades. It was first developed in early twentieth century, through the use of mustard gas in Second World War, which was shown to be a potent suppressor of hematopoiesis. The development of chemotherapy as a single agent or in combination led to an increase in the overall survival of cancer patients and, in some tumor types, promoting cure [2,3]. However, this therapeutic strategy is associated with AEs that may impact significantly the patient's quality of life. The toxicity seen with the use of cytotoxic chemotherapy is due to the lack of cell specificity of the drugs. AEs, such as nausea, vomiting, fatigue, diarrhea, alopecia, mucositis, infertility, among others, are landmarks for this kind of treatment, generating an entire stigma around cancer treatment [4].

The development of targeted therapies based on advances in molecular biology began in the 1960s through the study of growth factors. The first successful targeted therapy was imatinib, which was used for the treatment of chronic myeloid leukemia. The identification of a specific cellular protein or process that may serve as a target, not affecting other cells of our body, was a huge advance and has changed the natural history of cancer treatment [5].

Although targeted therapies have resulted in major advances in terms of quality of life, some patients experience severe toxicity. However, the toxicity profile and schedule of these agents are completely different from those observed with cytotoxic chemotherapy. Gastrointestinal AEs such as diarrhea, a wide range of skin lesions, cardiovascular diseases such as hypertension, and fatigue are the most frequently reported AEs that may impact negatively the quality of life and sometimes lead to discontinuation of therapy [6,7].

Targeted therapy, because of its generally oral route, seems to be an easier treatment to take. However, some AEs such as dermatologic affections may result in discontinuation in cancer therapy in approximately 30% of patients if left untreated [8]. Based on these findings, some studies have tried to use patient's preference and quality of life as a primary end point in order to make the best decision among different targeted therapies in which efficacy results are similar [9]. In addition, while this strategy has become widely used worldwide, clinicians had to learn how to manage the targeted therapy-related AEs in order to improve patient's quality of life during an oncologic treatment. With this goal, the concept of multidisciplinary care was then stimulated.

Unfortunately, targeted therapies were not enough to cure the majority of advanced solid tumors, opening new avenues to explore more effective cancer treatments. The concept that the immune system plays a role in tumor development and progression has been recognized for more than one century. Based on the elucidation of the mechanisms involved in the regulation of T-cell responses through immune checkpoints, a new class of agents called immune checkpoint inhibitors was developed [10]. The use of immune checkpoint inhibitors that are able to restore the T-cell response against tumor cells has demonstrated significant antitumor activity in different tumor types and has now become widely used.

Cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) are among the first checkpoints that have the ability to negatively regulate the T-cell immune response. Currently, several agents blocking these two pathways are available for different indications. Ipilimumab (anti-CTLA-4) was the first immune checkpoint inhibitor to be approved for melanoma treatment, resulting in a small subset of patients who achieve long-term responses. Among the inhibitors of the PD-1/PD-L1 axis, pembrolizumab was recently approved to treat melanoma. Similarly, nivolumab was approved for metastatic melanoma, non-small-cell lung cancer, and kidney cancer. Moreover, atezolizumab was approved for urothelial carcinoma and several others have been developed in early phase studies. Important research has been conducted in other tumor types and probably the list of agents and indications will rapidly increase in next few years. In addition, the dual checkpoint blockade with the

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combination of CTLA-4 and PD-1 inhibitors has shown improved efficacy compared with either CTLA-4 or PD-1/PD-L1 agents alone.

Importantly, this new class of agents has been associated with a distinct toxicity profile of immune-related adverse events (irAEs). As more as these agents become available for different indications, we are learning on how to recognize and manage treatment-related toxicities. In addition, the combination of immunotherapy agents or the combination of agents with distinct mechanism of action has resulted in a higher incidence of toxicities that directly impact patient's quality of life [11]. The pathophysiology of irAEs is not well understood. However, irAEs can affect any organ or system and are potentially fatal. Monitoring and correctly managing irAEs are critical to the patient safety and maintenance of performance status of patients receiving this therapy [12].

Overall, irAEs are observed in approximately 70% of patients and have a peculiar temporal pattern. After the first dose, skin changes are common in the form of erythematous maculopapular rash; after the second and third doses, gastrointestinal events are more evident, ranging from diarrhea to colitis and hepatotoxicity. After the third and fourth doses, there may be endocrine disorders, such as hypophysitis and thyroid dysfunction [13].

Usually, efficacy is the clinical outcome to be assessed in cancer research using response rate, progression-free survival, and overall survival as primary end points. However, toxicity profile and quality of life evaluations need to be incorporated in the decision-making process in order to balance the impact of the disease and its treatment on patient's quality of life. One phase III clinical trial comparing nivolumab versus everolimus in patients with metastatic renal cell carcinoma has shown that immunotherapy was associated with a better quality of life when compared with the targeted therapy [12]. In addition, another phase III trial comparing nivolumab versus docetaxel in patients with metastatic lung cancer who progressed to standard first-line therapy showed that the incidence of severe AEs was less frequent in patients receiving nivolumab compared to docetaxel [14]. Further studies are needed to evaluate the impact of this new treatment strategy in patient's quality of life.

Importantly, the cost of cancer treatments is rising rapidly and the financial toxicity is now a problem to be tackled. Recently, the American Society of Clinical Oncology developed a task force that may help health-care workers in providing high-quality cancer care, weighting the clinical benefit and the risk of severe toxicities. Scores have been developed in order to facilitate the definition of treatment value and it is important to highlight that toxicity profile of a specific treatment will be part of this judgment [15].

In summary, after cytotoxic chemotherapy and targeted therapies eras, we are living a third wave in cancer treatment. The immune-checkpoint inhibitors have resulted encouraging activity and durable clinical benefit has been observed. However, this therapeutic strategy has been associated with immune-related AEs that need particular attention. irAEs can affect any organ or system and require rapid recognition. Adequate diagnosis and appropriate management of these AEs are essential for maximizing the clinical benefit of these agents and to not negatively impact patient's willingness to be treated.

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Declaration of Interest

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