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Can functional status predict for lack of benefit for immunotherapy in advanced malignancies?

Despite rising survival rates, a cure for advanced malignancies continues to evade us. The advent of monoclonal antibodies that block the checkpoint on immune cells and unleashes it against the tumor cells provide a beacon of hope amidst the pessimism surrounding the management of a patient with metastatic cancer. With the advent of immune checkpoint inhibitors, unprecedented survival data is being reported in trials [1]. Promising efficacy data is getting churned out in several advanced malignancies [2]. This has led to an unbridled enthusiasm among patients, oncologists, pharmaceutical companies and patient advocacy groups. Consequently, there is a potential for the liberal use of checkpoint inhibitors in the community.

The growing use of novel treatments in everyday practice has led to questions regarding the financial impact of these drugs on the healthcare system and the benefits that patients may derive from them. Based on current estimates, the cost of adjuvant use of ipilimumab, a checkpoint inhibitor against CTLA-4 receptor, is nearly $400,000 per Quality Adjusted Life Year (QALY) saved, which is an index of quality and quantity of life lived [3]. In other words, the cost of one year with good health is $400,000. Most experts consider a QALY threshold of around $100,000 as being a cost-effective intervention [4]. If this is the cost involved with a potentially curative treatment, its use in the metastatic setting is most likely economically burdensome on the society. Currently, the poor cost-effectiveness of immunotherapy is an indisputable fact, whereas the efficacy of therapy is increasingly confirmed in various malignancies [5].

Therefore, identifying a biomarker that can predict for response to immunotherapy is of paramount importance. Mutational burden, tumor infiltrating lymphocytes, programed cell death ligand-1 (PD-L1) staining have all been evaluated as potential biomarkers for response to treatment [6]. Although there are several putative biomarkers, few have been consistently shown to have validity, concordance and precision. In this setting, we propose that we place a greater reliance on a patient's functional status in determining an indication for the use of immunotherapy, or rather for not using immunotherapy. Traditionally, use of cytotoxic chemotherapy in advanced malignancies has been reserved for patients with good functional status. Inappropriate use of chemotherapy in patients with poor functional status can have a detrimental effect on quality of life and survival. In fact, the American Society of Clinical Oncology recommends against the use of chemotherapy in patients with Eastern Cooperative Oncology Group performance status (ECOG) score of 3 and above, which is an index of poor functional status of a patient [7]. We suggest that a similar methodology be adopted by medical oncologists in determining appropriate use of immunotherapy. Furthermore, in our opinion, immunotherapy should not be used in patients with poor functional status until there is evidence for its effectiveness in such a clinical setting.

There are several reasons as to why we advocate for such a strategy in clinical practice. First, clinical trials of checkpoint inhibitors predominantly enroll patients with an ECOG status of 0 or 1. We do not have good quality clinical trial data on the use of immunotherapy in patients with an ECOG score of 2 or above. Second, the therapeutic effect of checkpoint inhibitors takes around 3 months to see a clinical response. Even in patients who are known to have mismatch repair deficiency, which is currently the only validated biomarker that predicts for response to immunotherapy, the average time to a clinical response is around 4–5 months [8]. Patients with a poor functional status often do not have the time to respond to checkpoint inhibitors. Their poor functional status reflects inferior outcomes compared to a patient who is functionally active. If functional status is used as a surrogate marker for life expectancy, we can postulate that patients who have impaired activity levels will likely do poorly with palliative immunotherapy. Third, only a fraction of patients in checkpoint inhibitor trials show a good response. Estimates on response to these drugs in patients vary depending on the primary site of disease, histologic subtype and molecular profile. Unfortunately, there could be a trend to use immunotherapy as a last resort for all types of advanced malignancies.

The argument against using performance status in predicting for lack of benefit of immunotherapy is based on the fact that these medications are generally more tolerable compared to chemotherapy [9]. However, decision to treat must not be based only on the tolerability profile of a medication. The use of any medications should either help a patient live longer or improve their quality of life. In our opinion, the use of immunotherapy in a patient with poor functional status achieves neither. For instance, a retrospective study of 91 patients with advanced melanoma who were treated with checkpoint inhibitors showed that patients with an ECOG score of 2–3 (n = 24) had a median overall survival of 1.8 months compared to 19.5 months for patients with an ECOG score of 0–1 (n = 58) [10]. The median overall survival in patients with an ECOG score of 2 was 2.3 months. Nearly, one in four patients in the study who received immunotherapy had an ECOG score of 2–3. While this is a small single-institution retrospective analysis, to our knowledge, it is the only study that has investigated this question. Nevertheless, it is a question that requires more scrutiny, and with great urgency.

No one disputes the fact that indiscriminate use of expensive medications is unsustainable to our public health system. As the era of checkpoint inhibitors unfolds, several questions are being investigated, including the timing and sequencing of checkpoint inhibitors, and using combinations of these medications with cytotoxic agents, but too often the financial cost to both the individual and the society are forgotten. Furthermore, checkpoint inhibitors are not without their repertoire of adverse effects. Analysis of trials suggests that these adverse effects are poorly reported and this further clouds our ability to guide management with an accurate estimation of therapeutic benefit and risk [11].

In addition to biomarkers such as MSI status and PD-L1 expression, the use of performance status to predict for lack of benefit for immunotherapy may help in controlling the rising cost of cancer healthcare. We advocate for a greater emphasis in studying the benefit of

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checkpoint inhibitors in patients with poor functional status. Such an effort could help identify biomarkers that predict for response to immunotherapy and justify its use in such patients. While the field of cancer medicine has progressed significantly in the past few decades, 'unchecked' use of checkpoint inhibitors with ever-increasing price-tags run the risk of not only diminishing the viability of our health care system, but also make physicians look like snake-oil salesman.

Conflicts of interest

No conflicts of interest to disclose.

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