Weighing up the pros and cons of immune checkpoint inhibitors in the treatment of melanoma

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The advent of monoclonal antibodies functioning as immune checkpoint inhibitors has changed the way advanced melanoma is treated. CTLA-4 inhibitors such as ipilimumab and the PD-1 inhibitors pembrolizumab and nivolumab all have an established place in the management of metastatic disease. They improve response rates, progression-free and overall survival compared with cytotoxic chemotherapy. In fact, ipilimumab was the first treatment ever to demonstrate an overall survival benefit in advanced melanoma, when compared with comparator arms of dacarbazine [1] and the vaccine gp100[2]. As such, even though associated with potentially serious toxicity, the pros clearly outweighed the cons.

More recent studies have established superiority of pembrolizumab and nivolumab over ipilimumab for overall survival, progression-free survival, objective response rate and tolerability. The combination of ipilimumab with nivolumab appears particularly potent, with a response rate equivalent to that of BRAF inhibition (58% vs 57% respectively)[3, 4]. Although overall survival data from the Phase III trial is not yet mature, progression free survival is significantly greater than ipilimumab (median 11.5 versus 2.9 months; HR 0.42; 99.5% CI, 0.31 to 0.57; P<0.001) and numerically greater than nivolumab (median 6.9 months). This is a very promising combination. Responses may be durable and lead to remission, even beyond cessation of therapy for toxicity, a situation that occurs in around a third of those treated [3].

The benefits of immune checkpoint inhibitors are clear and the disadvantages are usually manageable. This group of agents is associated with a particular set of side effects that warrant close attention and management. Immune-related adverse events

(irAEs) of grade 3 and 4 severity are more common with ipilimumab (20-27%) than with pembrolizumab (13%) or nivolumab (16%) [3, 5]. In a pooled analysis of nivolumab toxicity comprising over 500 patients, only 4% experienced select grade 3 or 4 irAEs, reinforcing the tolerability of this agent [6]. Combination treatment with ipilimumab and nivolumab carries a 55% risk of moderate to severe toxicity and in the absence thus far of OS benefit, this may be a deterrent for clinicans [3]. Nonetheless, the available evidence suggests that the majority of these irAEs are manageable with use of steroids and other immune-modulating drugs such as infliximab or mycophenylate where required. Generally the management of irAEs is pragmatic rather than evidence-based. More specific understanding of irAE pathogenesis may assist in rationalizing treatment choices and further research is needed in this area. From retrospective series, patient outcomes do not appear compromised as a result of reducing immune activation in the setting of toxicity [7, 8].

Although short to medium term toxicity across most organ systems appears manageable and is mostly reversible, there are some irAEs that may have permanent consequences. In the case of hypophysitis or diabetes, life-long exogenous hormone replacement may seem a small price to pay for survival, particularly as established management algorithms already exist for this. There is little published, however, on the outcomes of patients suffering, for example, severe neurological toxicity, and the extent to which such rare but serious problems may be reversible. Informed consent remains of paramount importance.

One challenge for every melanoma clinician is deciding how to sequence available therapies, particularly in patients whose tumours harbour a BRAF mutation. There are

no prospective data to guide this decision and unfortunately a validated discriminating biomarker for use in the clinic is lacking. An elevated LDH bodes poorly for response to ipilimumab in retrospective series [9, 10] and its trend early in treatment may also predict response to anti-PD-1 agents [11]. In patients with high volume disease of rapid tempo, or in those with multiple brain metastases, most clinicians prefer to commence a BRAF targeted therapy. In those with asymptomatic low volume soft tissue or lung metastases, most would choose an immune checkpoint inhibitor. The challenge of sequencing comes in for the patients who fall between these categories. There is a suggestion from subgroup analyses of the CheckMate-067 trial that combination ipilimumab and nivolumab over anti-PD-1 alone may be an advantage in patients with an elevated LDH [3]. One of the advantages in commencing treatment with an immune checkpoint inhibitor in patients whose melanoma is BRAF mutant is that on progression, they may be salvaged with dabrafenib or vemurafenib.

The balance of pros and cons with immune checkpoint inhibitors in the adjuvant setting is not currently as well defined. Ipilimumab improves recurrence-free survival in resected locoregional disease compared with placebo (47% versus 35% were recurrence-free at 3 years) and although an overall survival benefit has not yet been described, there is a clear signal for efficacy [12]. On this basis, the FDA has recently licensed ipilimumab at 10mg/kg for adjuvant use. Ipilimumab has not been compared with interferon, an older treatment but a standard of care in many parts of the world, however as many clinicians had already moved away from interferon prescribing the placebo arm remains representative of current practice. The reported 1% mortality rate dissuades some clinicians from recommending adjuvant ipilimumab, although our expertise in managing irAEs has improved since this study was undertaken. The

disclosure of possible toxicities takes on a different perspective in adjuvant patients as side effects may disproportionately impact health, relative to a lack of disease. Anti-PD-1 antibodies as adjuvant therapy are currently being evaluated in clinical trials (NCT02388906 and NCT02362594) and if one extrapolates from the advanced setting, they hold promise for greater efficacy and less toxicity than ipilimumab.

Cautious, balanced decision making is required when considering immune checkpoint inhibitors for treatment of patients with pre-exisiting autoimmune conditions or in organ transplant recipients. The literature is limited to case reports for use of ipilimumab in organ transplant recipients [13, 14], none of which describe any transplant rejection as a consequence. For people with pre-existing auto-immune conditions, small case series are also reassuring overall for the safety of ipilimumab [15, 16]. Now that the pembrolizumab and nivolumab are available outside of clinical trials, many clinicians will feel inclined to prescribe these when faced with progressive disease. Given the importance of PD-1 in antigen self-tolerance, there is arguably a greater risk of re-activation of an underlying autoimmune condition and rejection of an allograft. Positive publication bias for such cases has the potential to be misleading for clinicians.

On balance, the pros of immune checkpoint inhibitors in advanced melanoma eclipse the cons but in the adjuvant setting their acceptance into clinical practice may only be described as emerging. Novel inhibitors and combinations are currently being evaluated in clinical trials. As with all anti-neoplastic treatments, patient care is optimised by thoughtful decision-making and by having systems in place for early recognition and treatment of toxicity. We must continue working to determine optimal

sequencing of these agents, to define and validate therapeutic biomarkers, to deepen our understanding and refine management of immune-related toxicity. Clinicians have a responsibility to share information on outcomes of patients in whom immune activation has the potential to cause serious consequences such a transplant rejection and in those populations of patients where our understanding of efficacy is lacking, such as those with active brain metastases.

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