Editorial

Pembrolizumab for advanced hepatocellular carcinoma: tunnel at the end of the light

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Advanced hepatocellular carcinoma (HCC) is a dreary disease with limited therapeutic options and targeted therapy with sorafenib or regorafenib remain the only standard systemic treatment. These, however have modest efficacy at the expense of associated toxicity (1,2).

The fine balance between immune activation and tolerance in response to antigenic stimulation is modulated by the liver (3). It has been hypothesised that Chronic liver disease and HCC are the result of a dysregulation in an otherwise tightly controlled immunological network. HCC are therefore a heterogeneous group of tumors associated with inflammation and a suppressed immune environment; hence the rationale to evaluate immunotherapy in these tumors (3,4).

The immune checkpoint molecule programmed death-1 (PD-1) was first discovered by Ishida *et al.* in 1992 (5). They showed the gene encodes a receptor that "applies the brake to immune reaction". Being a negative regulator of T-cell effector mechanisms, stimulating the PD-1 receptor limits the immune responses against cancer. Mouse models have shown that blocking the interaction between PD-1 and its ligand significantly enhance immunity and thus, its antitumor effects (2,6). Building on this concept, monoclonal antibodies against PD-1, or its ligand programmed death-ligand 1 (PD-L1) were used successfully in the treatment of advanced melanoma in Japan (6). Furthermore, multiple trials have evaluated these drugs in the management of over 30 different cancers, with satisfactory outcomes (7,8). Phase I clinical trials in melanoma, non-small cell lung cancer and renal cell carcinoma using targeted immunotherapies with monoclonal antibodies against PD-1 and PD-L1 have shown promising results (7,8).

Pembrolizumab is a highly selective, humanized monoclonal antibody against PD-1 that blocks the negative immune-regulatory signalling of PD-1 receptor, thus reversing immune suppression induced by cancer cells (9). Binding of PD-1 on activated T-cells to PD-L1 or PD-L2 on tumor cells is blocked by the monoclonal antibody; creating an "immune escape" status. This results in the recovery of T-cell activity against on tumor cells. Dissimilar to other therapies, pembrolizumab restores and enhances the immune system, allowing it to regain its original ability to kill cancer cells (10,11).

Nivolumab, an anti-PD-1 monoclonal antibody, in a phase I/II trial was shown to be effective in advanced HCC with an objective response rate of 19% (12). The KEYNOTE-224, is the first Phase II study evaluating the role of pembrolizumab in advanced HCC patients previously treated with sorafenib (13). The primary endpoint of the trial was objective response using the response evaluation criteria in solid tumors (RECIST) criteria. Of the 104 patients enrolled for the study, objective response was observed in 18 (17%) patients, of whom 1 patient had complete response. Totally, 73% of the patients had treatment related adverse events, of these 15% had serious events, the commonest being liver injury related toxicity (rise in transaminases, immune mediated hepatitis etc.). There was one mortality directly attributable to the study drug. Being a phase II trial, the selection criteria was formulated keeping safety profile in mind; only patients with preserved liver function. (94% of the patients were Child Pugh Class A), were included in the study. The

median progression-free survival was 4.9 months and the median time to progression was 4.9 months. With a 12-month progression-free survival of 28%, the median overall survival was 12·9 months. At the end of the study period, 56 patients were still alive, with a 12-month overall survival rate of 54%. This is indeed a significant increase in survival amongst the cohort of patients who have had tumor progression on sorafenib. The absence of randomisation however does compromise the significance of these outcomes.

The majority of advanced HCC patients are likely to have associated background liver dysfunction, especially those in the eastern hemisphere, with its prevalence of viral hepatitis. These patients, unlike the cohort carefully chosen for the trial are unlikely to tolerate Pembrolizumab, given its propensity to cause immune mediated liver derangement.

Experience with Pembrolizumab in the post-liver transplant setting is very interesting (14). Despite patients being immunosuppressed, complete radiological remission of the metastatic lesions was achieved. Surprisingly, the native immune system boosted by the drug did not result in liver graft rejection or dysfunction. There have also been reports of severe immune mediated dysfunction in patients on Pembrolizumab, especially those with borderline background liver function (3,8,15).

This anecdotal report raises interesting questions on the drug's ability to achieve selective immune mediated destruction of tumour cells, while maintaining the immunosuppressive agents' immunomodulatory effects on the host immunity, thereby causing no immune mediated liver dysfunction. Extrapolating this phenomenon to patients with advanced HCC & liver dysfunction; could it be that the pathways of immune mediated tumour destruction and those of the body's native immune response are mutually exclusive? If biomarkers were identified to detect the presence of this alternate pathway, the indications and utility of pembrolizumab could potentially increase manifold to include even those with borderline liver function, who would otherwise have been excluded from its prescription.

Paradigm shifts in therapy based on immunotherapy are likely to improve the outcomes of treatment for HCC in the future. The KEYNOTE-224's authors' premise of exploring the role of biomarkers is well taken (14). Further analyses in this area is likely to shed more light and hopefully reduce the immune mediated adverse effects, thereby allowing its safe use in a wider subset of patients with advanced HCC. Further translational studies and clinical trials like the Keynote 240 trial are needed to further elucidate what's still early days of this promising drug's role in the management of a dismal disease (16).

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