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
eyear early days of this promising drug’s role in the management
of a dismal disease (16).

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Footnote
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References
hepatocellular carcinoma who progressed on sorafenib
treatment (RESORCE): a randomised, double-blind,
2. Kudo M. Systemic Therapy for Hepatocellular Carcinoma:
3. Ringelhan M, Pfister D, O’Connor T, et al. The
immunology of hepatocellular carcinoma. Nat Immunol
2018;19:222-32.
4. Prieto J, Melero I, Sangro B. Immunological landscape
and immunotherapy of hepatocellular carcinoma. Nat Rev
of PD-1, a novel member of the immunoglobulin gene
superfamily, upon programmed cell death. EMBO J
1992;11:3887-95.
6. Okazaki T, Honjo T. PD-1 and PD-1 ligands:
from discovery to clinical application. Int Immunol
7. Shih K, Arkenau HT, Infante JR. Clinical impact of
checkpoint inhibitors as novel cancer therapies. Drugs
8. Philips GK, Atkins M. Therapeutic uses of anti-PD-1 and
9. Ribas A. Tumor immunotherapy directed at PD-1. N Engl
10. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in
Tumors with Mismatch-Repair Deficiency. N Engl J Med
Pembrolizumab versus chemotherapy for PD-L1
2016;375:1823-33.


