



Immunotherapy and Transarterial therapy of HCC: What the interventional radiologist needs to know about the changing landscape of HCC treatment?

Jonathan Tibballs¹  and Warren Clements^{2,3,4} 

1 Department of Radiology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

2 Department of Radiology, Alfred Hospital, Melbourne, Victoria, Australia

3 Department of Surgery, Monash University Central Clinical School, Melbourne, Victoria, Australia

4 National Trauma Research Institute, Melbourne, Victoria, Australia

J Tibballs MBBS, FRANZCR; **W Clements** MBBS, BBiomedSc(Hons), FRANZCR, EBIR-ES, FCIRSE.

Correspondence

A/Prof Warren Clements, Department of Radiology, Alfred Health 55 Commercial Road, Melbourne, Vic., 3004
Email: w.clements@alfred.org.au

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer worldwide.¹ The incidence of HCC has increased in developed countries and is commonly associated with non-alcoholic fatty liver disease, chronic hepatitis C infection and alcohol overuse.^{1,2} Carville *et al.* showed that between 2004 and 2013, the 5-year survival rate for patients with HCC in Victoria was 16%, and this increased from a rate of only 5% between 1984 and 1993.³ There have been disproportional effects from HCC on Aboriginal and Torres Strait islander people as well as those in regional locations.^{2–5}

Treatment of HCC should be decided in a multidisciplinary meeting (MDM) setting which includes the presence of an Interventional Radiologist.⁶ Many centres use international guidelines to guide treatment, and the Barcelona Clinic Liver Cancer (BCLC) staging system is a

Abstract

Hepatocellular carcinoma (HCC) is the fourth most common cancer worldwide and its incidence is increasing in Australia. Transarterial therapy, predominantly transarterial chemoembolization (TACE) but increasingly transarterial radioembolization (TARE), plays an important role in patients with intermediate-stage disease and preserved liver function. However, despite advances in TACE, TARE and adjunctive procedures, overall survival has only modestly increased over the last 20 years. Immunotherapy has emerged as a newer cancer treatment and uses antibodies directed at checkpoint inhibitors to upregulate T-cell mediated tumour-specific death. These drugs have been shown to increase survival in patients with HCC and have changed the landscape for advanced disease. Trials are now ongoing combining transarterial therapy and immunotherapy. This manuscript introduces these trials and interventional radiologists should be aware of the changing landscape so that they can partner with immunotherapy and remain relevant in the HCC multi-disciplinary group as immunotherapy use increases.

Key words: embolization; HCC; immunotherapy; SIRT; TACE.

commonly used algorithm.⁷ This recommends the use of TACE for patients with intermediate-stage disease and preserved liver function.⁷ The recent updated version of the BCLC guidelines for the first time also includes Selective Internal Radiation Therapy (SIRT)/Transarterial Radioembolization (TARE) in its algorithm.⁸

However, it has been acknowledged that TACE, as an umbrella term, is actually a heterogeneous procedure at the patient level as operators vary markedly with use of different chemotherapeutic and embolic agents, in addition to the lack of standardisation of the technique between different centres and different countries.⁹ As a result, overall survival after TACE varies and is said to be between 20 and 25 months.¹⁰ In recent years, different alternatives to TACE have emerged including the use of drug-eluting beads (DEB-TACE) and radioembolization (SIRT, TARE, or Y-90 radioembolisation).^{11,12} While DEB-TACE is known to be well tolerated, there has not been an

established survival benefit compared with conventional TACE.¹¹ Similarly, there is an important role for radioembolization in selected patients, but it has not been shown to improve overall survival for all patients with intermediate HCC.¹² As with TACE, SIRT is subject to variation in technique and particularly dosimetry that can significantly affect HCC treatment outcomes. This was clearly demonstrated in the SARAH study,¹³ a prospective randomised control trial of sorafenib versus SIRT in patients with advanced HCC. The trial was designed to show superiority of SIRT over sorafenib, but although the SIRT arm showed significantly increased tumour response, fewer complications and improved quality of life, it failed to meet its primary end point of improved overall or progression-free survival. Limitations of this study are well known with 22% of patients randomised to SIRT not receiving SIRT and suboptimal dosimetry initially based on the BSA model and median patient doses of only 0.99–1.85 GBq per patient. The advent of personalised dosimetry is already shown to improve tumour response rates.¹⁴ Other newer TACE-adjuncts have also developed including smaller microcatheters and balloon-catheters.¹⁵ The use of fluoroscopy aids such as cone-beam CT and tumour guidance has also emerged.

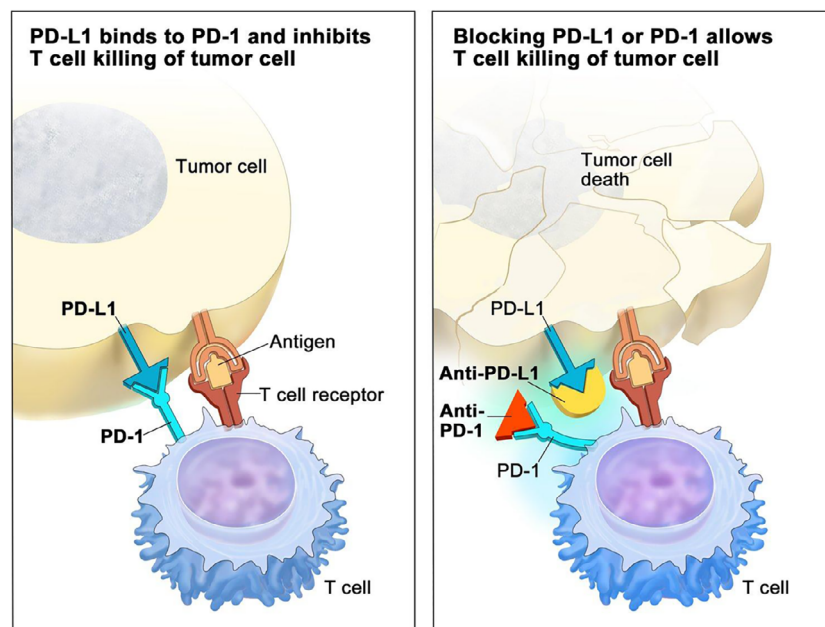
However, although modifications in TACE technique and its variations can result in excellent results in selected patients, overall survival rate increases have been only modest and it is clear that TACE is not a cure for HCC with median survival rates varying from 20 to 25 months in randomised controlled trials.¹¹ There are likely to be numerous factors contributing to this; however, a major influence is likely the underlying biology of the tumour, and the presence of background widespread hepatocellular damage.¹

Systemic therapy and immunotherapy in HCC

The first drugs approved for use in advanced HCC were kinase inhibitors.¹⁶ The most widely known is sorafenib which is a tyrosine kinase (TK) inhibitor that inhibits multiple growth factor receptors.¹⁷ While sorafenib has been shown to improve mean overall survival rate for patients with advanced-stage HCC, it is poorly tolerated due to side effects with the most common diarrhoea, fatigue, skin changes and alopecia.¹⁷ The REFLECT study¹⁸ compared another tyrosine kinase inhibitor, lenvatinib, with sorafenib, and found it to be non-inferior. Lenvatinib achieved a non-significant increase in overall survival (OS) from 12.3 months with sorafenib to 13.6 months with lenvatinib, and improved progression-free survival (PFS) from 3.6 months with sorafenib to 7.3 months with lenvatinib, but both drugs demonstrated significant levels of toxicity.

Compared with established cancer therapies, immunoncology or immunotherapy offers a different treatment approach to TK inhibitors. The concept is to engage the immune system to recognise tumour cells and to provide tumour death through innate immunological mechanisms.¹⁹ Immune checkpoints are regulators of the immune system. They prevent the immune system from attacking cells indiscriminately. However, some cancers can protect themselves from attack by stimulating immune checkpoint targets. Programmed cell death protein 1 (PD-1) is an inhibitory receptor that is expressed on some tumour cells and causes down regulation of the immune system by reducing T-cell activity. Anti-PD-1 monoclonal antibodies block the PD-1 receptor, so the T cells are no longer inhibited, and therefore, activate the immune response against the tumour (Fig. 1).

Fig. 1. Immune checkpoint inhibitor. Checkpoint proteins, such as PD-L1 on tumour cells and PD-1 on T cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumour cells in the body (left panel). Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumour cells (right panel).



Modern immunotherapy began as monoclonal antibody preparations and included trastuzumab (for breast cancer) and rituximab (for non-Hodgkin's lymphoma). However, in the late 1990s, it was observed that antibodies play an important role in priming the T-cell mediated immune response and this led to a more promising range of checkpoint inhibitors including those targeted at ligands such as programmed cell death-1 (PD-1), programmed cell death ligand-1 and -2 (PD-L1 and PD-L2), and cytotoxic T-lymphocyte antigen number 4 (CTLA-4). One of the most high-profile roles for immunotherapy is in the treatment of advanced Melanoma.²⁰ Ipilimumab (a CTLA-4 inhibitor) was the first checkpoint inhibitor to show an improvement in overall survival in a randomised, controlled phase III trial in advanced melanoma leading to FDA approval in 2011.^{21,22} Since then, laboratory and translational research has expanded exponentially in the immunotherapy space on a range of different cancers.

Immunotherapy and HCC

In 2017, FDA approval was granted in the United States for the treatment of advanced HCC after the CheckMate 040 trial (phase 1/2, open-label, non-comparative) showed promising results on the role of nivolumab, a PD-1 inhibitor. The authors concluded that the drug was safe in the setting of Hepatitis B and C co-infection and provided similar response and durability to advanced-stage treatments in other cancers.^{23,24} This led to the CheckMate 459 study which was a randomised phase 3 study comparing sorafenib and nivolumab in patients with advanced disease. The study showed a higher median overall survival in patients taking nivolumab (16.4 vs. 14.7 months).^{24,25} The Keynote-224 trial was a phase 2 trial assessing pembrolizumab (PD-1 inhibitor) in patients who progressed after sorafenib or were intolerant, showing a median overall survival of 12.9 months and median progression-free survival of 4.9 months.²⁶

As a natural progression from monotherapy, combination therapy has also been investigated. The ImBrave150 trial, published in the New England Journal of Medicine in 2020, randomised patients to sorafenib or combination atezolizumab (PD-L1) and bevacizumab (anti-vascular endothelial growth factor monoclonal antibody). Progression-free survival was significantly longer in patients taking atezolizumab-bevacizumab (median 6.8 months vs. 4.3 months) and this has become the benchmark of therapy for advanced HCC in Australia.²⁷ There are a range of newer studies currently recruiting in this area including the HIMALAYA trial assessing combination tremelimumab (CTLA-4) and durvalumab (PD-L1) as well as CM459, SHR-1210, RATIONALE-301 and LEAP-002 just to name a few.²⁴

Immunotherapy and transarterial therapy for HCC—what is on the horizon?

Trials on the role of systemic immunotherapy have not just been limited to advanced disease but are now extending

towards patients with early or intermediate-stage disease who are suitable for existing treatments including TACE or SIRT. These trials have been based on early laboratory data highlighting the importance of interventional strategies in releasing tumour antigen and engaging tumour-specific T-cells.²⁸ To highlight this, Pinato *et al.* assessed patients who underwent surgery for HCC, and compared the expression of immune markers in those who had pre-procedure TACE. In the 58 patients with pre-procedure TACE, intra-tumoral samples showed significantly lower expression of CD4⁺/FOXP3⁺ and CD8⁺/PD-1⁺, both predictors of improved recurrence-free survival. In a subset of 24 patients with viable tumour on histology, those treated with TACE demonstrated significant upregulation of interferon-regulated transcription factor 2 (IRF2) which is a transcriptional repressor of PD-L1 and regulator of a number of components of the Major Histocompatibility Complex-I pathway.²⁹ This suggests TACE increases intra-tumoral inflammation and may have a role in activating initial tumour antigen expression which could augment immunotherapy if given in combination.

To assess this in a real-world scenario, the Emerald-1 study (AstraZeneca)³⁰ began recruiting in 2018 and is a phase 3 study comparing combination TACE treatment with either systemic placebo, durvalumab, or durvalumab-bevacizumab. Similarly, the TACE-3 study (Bristol-Myers Squibb)³¹ has been recruiting since 2019 and is comparing TACE to combination TACE-nivolumab. The LEAP-012 study (Merck Sharp & Dohme Corp)³² has been recruiting since 2020 and compares TACE with combination TACE lenvatinib-pembrolizumab. Results from these three trials have not yet been released as the trials are still recruiting.

Similar interest is being shown in the area of TARE. Boston Scientific has recently launched the ROWAN study—a global open-label, prospective, multi-centre, randomised, Phase II trial with two treatment arms designed to assess the safety and efficacy of TheraSphere administered before initiation of durvalumab with tremelimumab in HCC patients not eligible for or who have declined treatment with resection and/or ablation or liver transplant.³³

The study of the safety and antitumoral efficacy of nivolumab after SIRT for the treatment of patients with HCC (NASIR-HCC) is a phase 2 multi-centre, open-label, single-arm study of the safety and antitumoral efficacy of nivolumab in combination with RE using SIR-Spheres for the treatment of patients with HCC that are candidates for locoregional therapies. This demonstrated an overall response rate (ORR) of 40% comprising 12.5% complete response and 27.5% partial response with an acceptable safety profile.³⁴

The following investigator led trials involving resin spheres (SIRT) are also underway (Personal communication - Sirtex Medical Ltd. Pty):

STRATUM: SIRT-Y90 Followed by atezolizumab plus bevacizumab vs. SIRT Y90 followed by placebo in Advanced Hepatocellular Carcinoma. Multi-national, double-blind, placebo-controlled, parallel-arm,

randomised, phase II trial comparing efficacy and safety of SIRT followed by atezolizumab plus bevacizumab vs. SIRT followed by placebo.

Y90-Radioembolisation in Combination with Nivolumab in Asian Patients with Advanced Hepatocellular Carcinoma. Phase II Open-Label, Single-Centre, Non-Randomised Trial Evaluation of response.

sIMMBOLIZE: selective Immuno-Embolization with SIR-Spheres. Prospective Single Arm.

Evaluate clinical activity of atezolizumab/bevacizumab in combination with SIRT as first-line therapy.

IMMUWIN: A Phase II study of immunotherapy with durvalumab (MEDI4736) and tremelimumab in combination with either SIRT or TACE for intermediate-stage HCC.

What is the future?

As with the results of the ImBrave150 trial, it is likely that combination therapy will be more effective than monotherapy.³⁵ In the setting of HCC, this may be any combination of monoclonal antibody, immune checkpoint inhibitor and interventional-oncologic treatment such as TACE or SIRT/TARE. Practically for IRs, it is important for us to stay relevant with co-therapies given the upregulation of T-cell mediated immune response after TACE and the important role in ensuring targeted immunotherapy. Transarterial delivery of immunotherapy is a potential logical progression of combination therapy and may enhance local anti-tumour effects whilst minimising the current significant systemic side-effect profile of many of the currently available immunotherapy agents. It is, therefore, essential that IRs are aware of these principles and are involved in the design and execution of trials and make immunotherapy part of IR treatment at the MDM.

As shown by the sponsorship of the above trials, major pharmaceutical companies are investing heavily in an area with significant growth potential. Investment is also likely to increase through grants and these will both drive further growth in positive non-TACE outcomes for HCC. Some are even predicting the potential for curative intent with immune checkpoint inhibitors.³⁵ While this may be a sizeable leap from existing evidence, it is certainly a positive step for HCC treatment, and one which IR needs to be associated with to establish the potential for significant public health influence of our specialty as we consider specialty recognition in Australia and New Zealand.

As has always been the issue with transarterial therapy, treatments and newer trials will be made more robust by reliable standardisation of TACE and optimisation of dose in SIRT, work that has been heavily driven by CIRSE and SIR with their Standards of Practice guidelines and more recently the CIRSE initiative of the International Accreditation System for Interventional Oncology Services (IASIOS). Standardisation will allow for improvements in interpretation of transarterial therapy outcomes, and this will, in turn, assist with future immunotherapy combination.

Change is on the horizon and current treatment algorithms such as BCLC are imminently out-of-date with newer systemic therapies, combination immunotherapy and other changes such as combination transarterial/immunotherapy. It is the belief of the authors that IRs should keep up to date with the outcomes of trials such as Emerald-1, TACE-3, LEAP-012, NASIR-HCC and STRATUM, partner with immunotherapy, and be involved in the changing landscape of intermediate-advanced HCC treatment.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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