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Review Article

Immunotherapy Combined with SBRT for Patients with Hepatocellular Carcinoma–A Review

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ABSTRACT

Immunotherapy has been proven to act synergistically with radiotherapy to prime the immune response against the immunosuppressive tumour microenvironment. This strategy may improve local control and systemic control through the abscopal effect. Stereotactic Body Radiation Therapy (SBRT) has provided excellent local control rates in Hepatocellular Carcinoma (HCC). Retrospective and prospective studies involving advanced-stage HCC patients support combining SBRT with immune checkpoint inhibitors. This review aims to discuss the mechanisms by which immunotherapy can improve the efficacy of SBRT in patients with hepatocellular carcinoma. The review will outline current guidelines for HCC treatment, the rationale for combining immunotherapy and radiotherapy, the impact of the HCC tumour microenvironment and the potential for SBRT to elicit an abscopal effect.

Keywords: Immunotherapy; Immune checkpoint inhibition; Hepatocellular carcinoma; Stereotactic body radiotherapy; Radiotherapy

INTRODUCTION

Background

Hepatocellular Carcinoma (HCC) is the most common form of liver cancer and is a leading cause of cancer mortality in men worldwide. The burden of HCC is set to increase over the next couple of decades, with an estimated 1.3 million deaths in 2040. The increasing prevalence of non-alcoholic steatohepatitis, obesity, alcohol consumption and hepatitis infection is set to contribute to this increase. Hepatitis B and C are responsible for most cases of HCC. This cancer's aggressive and asymptomatic nature means most patients are diagnosed at a late stage, where the prognosis is severely reduced compared to early detection. The Barcelona Clinic Liver Cancer (BCLC) staging system is used to stage HCC and provide treatment guidelines. Stage 0/A is for singular nodules less than 3 cm, stage B is for multinodular disease and stage C is for advanced disease that consists of portal invasion or extrahepatic spread. Early-stage curative treatment involves surgical resection, liver transplantation or ablative therapy, which only approximately 20% of patients are eligible for. The advanced stage at presentation, lack of liver donors, poor liver function (determined by Child-Pugh score) and complex tumour location are some reasons these curative treatment options are not feasible [1].

Traditionally External Beam Radiation Therapy (EBRT) has not been included as a treatment option in the BCLC guidelines. This is due to classical and non-classical Radiation-Induced Liver Disease (RILD). Previously, patients received whole liver irradiation for palliative purposes. The high dose to the entire liver led to side effects such as hepatomegaly, anicteric ascites and elevated serum transaminase which can limit the treatment course and lead to severe chronic effects. Modern-day treatment planning and highly conformal radiotherapy techniques have increased the use of radiotherapy in the form of SBRT for various complex presentations of HCC. SBRT is used for radical treatment of smaller tumours, as bridging therapy for subsequent liver transplantation and as palliative treatment when the advanced disease has led to Macrovascular Invasion (MI). Portal Vein Tumour Thrombus (PVTT) is a form of MI with poor median survival of approximately three months without treatment.

SBRT is a precise treatment that delivers a higher radiation dose than conventional radiotherapy to a conformal tumour area in fewer fractions. This steepens the dose gradient to the tumour

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and minimises radiation dose to the surrounding liver parenchyma. SBRT is indicated in guidelines for when curative options, radiofrequency ablation or TACE, cannot be performed due to contradictions where the treatment is unfeasible. A highly effective 2-year local control rate of 90-100% was documented from a range of phase II clinical trials summarised by Y Matsuo et al. According to propensity score analysis, SBRT is greater than TACE and comparable to RFA. This high local control rate and minimal toxicities have expanded its role in treating HCC. The landmark RTOG 1112 phase III trial results showed a greater efficacy when SBRT was combined with Sorafenib (a tyrosine kinase inhibitor) compared to the drug alone. Several meta-analyses of SBRT combined with TACE or Sorafenib have also shown increased overall survival rates and improved outcomes. Limited evidence exists to support SBRT immunotherapy combinations in patients with HCC, apart from retrospective studies, which are prone to confounding, recall and selection bias [2].

Immunotherapy has expanded the potential mechanisms by which tumour cells can be targeted and destroyed. Treatment using immunotherapeutic drugs utilises the host's immune system to increase the recognition and destruction of tumour cells. Drugs targeting Immune Checkpoint Inhibition (ICI) have become first-line treatments for many cancer types. Programmed Death Ligand 1 (PD-L1), Programmed Cell Death Protein 1 (PD-1) and Cytotoxic T Lymphocyte Protein 4 (CTLA-4) are common targets for ICI by monoclonal antibodies. These immune checkpoints regulate the host immune system to prevent an overactive immune response against self-antigens, this enables peripheral self-tolerance.

The interaction of the CTLA-4 receptor on the surface of T cells with CD80/CD86 protein on Antigen-Presenting Cells (APCs) suppresses the immune response. CTLA-4 has a greater binding affinity than the CD28 surface molecule, which also binds to CD80/CD86 resulting in co-stimulation. The binding of CTLA-4 prevents a co-stimulatory signal required for T-cell activation and proliferation. CTLA-4 on the surface of T regulatory cells (Tregs) is also involved with the suppression of the function of T cells. A similar inhibitory interaction occurs when the PD-1 receptor on the surface of many classes of immune cells binds to the PDL-1 receptor on the surface of tumour cells and APCs. Overall, this reduces the survival of T cells and the production of key immune-modulating cytokines such as Interferon-Gamma (IFN-γ). PD-1 expression is associated with exhausted T cells, which have been repeatedly activated and provide a weaker immune response. Tumour cells use the expression of these immune checkpoints to evade the immune response. Over-expression of PD-1 on the surface of solid tumour cells is associated with a poorer prognosis. Therefore, immune checkpoint inhibitors prevent T cells' negative regulation, leading to greater activation and targeting of tumour cells [3].

LITERATURE REVIEW

The rationale of radiotherapy and immunotherapy combination

SBRT, although having a higher dose per fraction than EBRT, has similar immune-modulating effects. Radiotherapy causes simultaneous changes in the Tumour Microenvironment (TME), which primes the immune system against tumour cells. It is said to transform 'cold' environments with a lack of T cell infiltration to 'hot' environments with many activated T cells specific to irradiated tumour cells. This response is usually localised however can occur distally due to the abscopal effect. This is defined as tumour regression in non-irradiated metastatic tumour sites post-radiotherapy [4].

Radiotherapy enhances the tumour-specific immune response by activating many pathways. Radiotherapy causes necrosis and apoptosis of tumour cells. This destruction releases Damage-Associated Molecular Patterns (DAMPS) such as cytosolic RNA and ATP. This cell debris is taken up by APCs and presented on Major Histocompatibility Complex class 1 (MHC-1) molecules on their surface as Tumour-Associated Antigens (TAAs). This leads to the activation of cytotoxic T cells (CTLs) against tumour cells that express these antigens. Tumour cells downregulate the display of MHC-1 molecules as an immune escape mechanism. Radiotherapy causes increased MHC-1 and calreticulin expression, helping CTLs recognise and destroy tumour cells.

Modulation of the innate immune response also occurs alongside the adaptive response. FAS is a death receptor that induces apoptosis when bound to the FAS ligand or an agonist antibody. Radiotherapy has been shown to increase the expression of FAS in tumour cells. Radiotherapy produces DNA micronuclei and mitochondrial genome DNA in the cytoplasm of cancer cells. This double-stranded DNA binds to cyclic GMP-AMP Synthase (cGAS), which activates it, to form the second messenger 2'3'-cyclic GMP-AMP (cGAMP). cGAMP then binds to the Stimulator of Interferon Genes (STING) dimers causing a conformation change. A series of further steps enables Interferon Regulatory Factor 3 (IRF3) to induce the production of type 1 Interferons (IFN). IFN-1 production is essential for the maturation of Dendritic Cells (DCs) and the priming of CD8+ T cells against tumour antigens.

The TME resists the infiltration and proliferation of activated T cells. Stroma fibroblasts lead to lymphocyte exclusion and Naito et al., showed that a lack of CD8+ infiltration was associated with poorer outcomes. Competition for metabolites such as glucose and glutamine in the TME further disrupts the infiltration and survival of T cells. Radiotherapy counters this poor infiltration by increasing the expression of chemokines and adhesion molecules to promote the attraction and infiltration of CTLs. Expression of Vascular Cell Adhesion protein-1 (VCAM-1) and Intracellular Adhesion Protein-1 (ICAM-1) increase the infiltration, whereby CXCL10/CXCL16 attract CD8 and CD4 positive T cells to the irradiated tumour sites [5].

Although radiotherapy is shown to potentiate the immune response, it is regarded in literature to have an immunosuppressive effect. Studies have concluded that radiotherapy increases the level of Tregs in the TME. Radiation promotes the production of IL-10, converts CD4+ T cells to Tregs and increases TGF-β levels. IL-10 and TGF- β, through the Signal Transducer and Activator of Transcription pathway 3 (STAT3) and SMAD signalling pathways, increase the differentiation, development and expansion of Tregs. This creates an even greater immunosuppressive TME post-irradiation. Treg cells exert this immunosuppressive effect in several ways. Tregs express CTLA-4 checkpoint proteins to inhibit co-stimulatory signalling, consume IL-2 to limit the activation and proliferation of effector T cells and produce cytokines IL-10 and TGF-β to inhibit T cell function [6].

Radiotherapy promotes the conversion of Tumour-Associated Macrophages (TAMs) to express an M2 phenotype, promoting the progression and survival of tumour cells. TAMs are attracted to the hypoxic TME following radiation exposure due to the release of Chemokine Ligand 2 (CCL2) and Colony-Stimulating Factor 1 (CSF1). These chemokines also recruit Myeloid-Derived Suppressor Cells (MDSCs), which cause immunosuppression by suppressing the function of CTLs, natural killer cells and anti-tumour B cells. MDSCs promote the survival of Tregs and M2 TAMs and stop the cross-priming of dendritic cells to activate CTLs. The infiltration of MDSCs is a crucial factor contributing to radiation resistance.

In summary, radiotherapy can enhance the anti-tumour immune response, but equally, there is a more dominant immunosuppressive effect. Therefore, adding immunotherapeutic drugs like immune checkpoint inhibitors to radiotherapy can negate the immunosuppressive effect. The balance shifts towards creating a ‘hot’ TME with high immunogenicity whereby T cells are primed against tumour cells without the subsequent inhibition and T cell exhaustion following radiotherapy. This combination could take advantage of the effective local control rates of SBRT and promote this effect further in situ and systemically [7].

HCC tumour microenvironment

The Tumour Microenvironment (TME) of HCC is generally regarded as immunosuppressive. Hepatic portal circulation constantly exposes liver sinusoidal endothelial cells to various bacterial antigens. This prevents an excessive, unnecessary immune response. There is an increased expression of PD-L1 receptors and increased production of immunosuppressive cytokines such as TGF-β and IL-10 by Kupffer cells. Chronic inflammation due to infection by hepatitis B or C can also potentiate this immune suppression by producing proinflammatory cytokines, forming cirrhotic liver tissue and remodelling of the liver microenvironment to a preneoplastic state. The TME of HCC contains CD4 T helper cells which have differentiated into Th2 and Th17 types in higher proportion than non-cancerous tissue. These collectively produce abundant immunosuppressive cytokines such as TGF-β, IL-10, IL-4 and IL-17, promoting the polarisation of TAMs into the pro-tumour M2 type and facilitating microvascular invasion. The cytolytic activity of NK cells and cytotoxic T cells was also shown to be inferior compared to non-cancerous tissue. The HCC TME contains an abundance of T regs, Myeloid-Derived Suppressor Cells (MDSCs) and a lack of infiltration of activated T cells. ICI is a strategy used to counter this immunosuppression [8].

SBRT-Specific effects on tumour microenvironment

The higher dose and relatively shorter number of fractions of SBRT differentiate it from conventional EBRT. SBRT creates antigenicity through the even larger release of DAMPS and TAA presentation. Immune activation and upregulation of immune cell surface markers such as FAS are also dose-dependent. The precision of this technique minimises the radiation dose ‘splash’ to normal tissue. This includes lymphatics, allowing for greater migration of DAMPs and cross-presentation to DCs in the lymph nodes. The effects of SBRT on immune cells of HCC TME have been tested pre-clinically. L Tian et al., showed an increase in peripheral CD3+CD56+NKT-like cells post-SBRT. This increase was associated with a higher overall survival, possibly due to the prominent anti-tumour effect exhibited by this cell type [9].

DISCUSSION

Radiotherapy and the abscopal effect

Out-of-field failure is a key reason why HCC treatment fails long term. Therefore, research into treatments that reduce metastatic tumour burden is of interest. Immunogenic cell death from high-dose radiation produces DAMPs that migrate to lymph nodes. This enables the priming of CTLs against these antigens presented by DCs to stimulate the anti-tumour response. These activated immune cells can move to sites of distal tumours to eradicate specific tumour cells and cause an abscopal effect. This only occurs if primed T cells can overcome the differing immunosuppressive TME of other tumour sites, which can act as a barrier to these newly activated cells. Radiotherapy can promote the infiltration of cytotoxic T cells and cytokines such as IFN-γ into the new TME. IFN-γ is critical in the new TME to induce priming of cytotoxic T cells. Reduced level of MDSCs systemically has been associated with the abscopal effect pre-clinically. Limited clinical evidence is available currently documenting the abscopal effect in patients [10].

CONCLUSION

The use of low-dose or high-dose radiation to induce the abscopal effect has been debated in the literature. SBRT uses higher doses which can liberate a greater number and variety of DAMPs meaning T cell priming against a large variety of TAAs. However, a greater abscopal effect was seen when 8Gy in 3 fractions was delivered to breast cancer xenografts compared to 20Gy in a single fraction (concurrently with a CTLA-4 inhibitor). This could result from doses greater than 12-18Gy activating Trex1, which degrades cytosolic DNA, attenuating the production of type 1 IFNs from the cGAS-STING pathway. One paper suggests the combination of higher-dose hypo-fractionated radiotherapy and low-dose radiotherapy to induce the maximum abscopal effect. With the rationale that low-dose radiotherapy can increase the production of T cell attractive cytokines, generate M1 type tumour associated macrophages, increase the ratio of CD8+ to T cells and modulate a range of molecular pathways that stimulate the systemic anti-tumour response.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

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CONFLICTS OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

Ajay Patel first and only author.

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REFERENCES

1. Rumgay H, Arnold M, Ferlay J, Lesi O, Cabasag CJ, Vignat J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. J Hepatol. 2022;77(6):1598-1606.
2. Huang DQ, Singal AG, Kono Y, Tan DJ, El-Serag HB, Loomba R. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. Cell Metab. 2022;34(7):969-977.
3. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol. 2023;79(2): 516-537.
4. Yang C, Zhang H, Zhang L, Zhu AX, Bernards R, Qin W, et al. Evolving therapeutic landscape of advanced hepatocellular carcinoma. Nat Rev Gastroenterol Hep. 2023;20(4):203-222.
5. Que J, Lin CH, Lin LC, Ho CH. Challenges of BCLC stage C hepatocellular carcinoma: Results of a single-institutional experience on stereotactic body radiation therapy. Medicine. 2020;99(32):e21561.
6. Colagrande S, Inghilesi AL, Aburas S, Taliani GG, Nardi C, Marra F. Challenges of advanced hepatocellular carcinoma. World J Gastroenterol. 2016;22(34):7645-7659.
7. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76(3):681-693.
8. Lewis S, Dawson L, Barry A, Stanescu T, Mohamad I, Hosni A. Stereotactic body radiation therapy for hepatocellular carcinoma: From infancy to ongoing maturity. JHEP Rep Innov Hep. 2022;4(8): 100498.
9. Lin H, Wu H, Cong N, Liu B, Liu C, Han D. Transarterial chemoembolization followed by radiotherapy versus sandwich treatment for unresectable or ablative hepatocellular carcinoma. Technol Cancer Res Treat. 2020;19.
10. Roberts HJ, Wo JY. Stereotactic body radiation therapy for primary liver tumors: An effective liver-directed therapy in the toolbox. Cancer. 2022;128(5):956-965.