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Immuno-oncology and interventional oncology: a winning combination. The latest scientific evidence

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Abstract. – OBJECTIVE: Interventional oncology (IO) is an emergent field in interventional radiology that can be considered the fourth pillar of oncology. Interventional oncology has the unique capability to treat malignancy in a loco-regional fashion enabling curative (percutaneous ablation), disease stabilization (intra-arterial chemo/radioembolization), and palliative treatment (such as biliary drainage or nephrostomy).

The whole arsenal of IO acts by inducing necrosis and apoptosis, with interactions with the tumour's microenvironment potentially crucial for oncological outcomes.

Considering that tumour's microenvironment is a pivotal target for both immuno-oncology and interventional-oncology, the interactions between these two anti-tumour weapons must be investigated to understand their synergy. Interestingly, substantial efforts have been directed to understand which technique combinations are best for specific tumours.

This review article summarizes the latest scientific evidence highlighting the future prospective of this winning combination, integrating evidence-reported literature and experience-based perceptions.

Key Words:
Interventional oncology, Immunotherapy, Ablation, Chemoembolization, Checkpoint, Immunomodulation, Radioembolization, Immuno-oncology.

Abbreviations

IO: interventional oncology; DCC: disseminated cancer cells; CTLA: cytotoxic T-lymphocyte-associated protein; RFA: radiofrequency ablation; HCC: hepatocellular carcinoma; TAA: tumour associated antigen; IFN-γ: interferon gamma; ELISPOT: enzyme-linked immunospot; CpG: cytosine triphosphate deoxynucleotide followed by guanine triphosphate deoxynucleotide; CD4+: cluster

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of differentiation 4; CD8+ cluster of differentiation 8; NSCLC: non-small cell lung cancer; TACE: transarterial chemoembolization; CEA: carcinogenic embryonic antigen; HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; IL-1: interleukin-1; IL-6: interleukin-6; NF-κβ: nuclear factor kappa β; TNF-α: tumour necrosis factor-α; MW: microwave; HIFU: high focal ultrasound; LiTT: laser-induced thermo therapy; IRE: irreversible electroporation; GM-CSF: granulocyte-macrophage colony-stimulating factor; TNFRI: tumor necrosis factor receptor type I; CRP: c-reactive protein test; RLU: relative luminescence units; Poly-ICLC: polyriboinosinic-polyribocytidylic acid stabilized with poly L-Iysine and carboxymethylcellulose; AFP: alpha fetoprotein; VCAM-1: vascular cell adhesion molecule-1.

Introduction

A Potential Interactions Between Immuno-Oncology and Interventional Oncology

The traditional hallmarks of cancer, published in 2000 by Hanahan and Weinberg[1], include: sustaining proliferative signalling, evading growth suppression, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death. These hallmarks were updated in 2011[2], due to the increasing focus on immune system effects, by including: deregulating cellular energetics, avoiding immune destruction, genome instability and mutation, and tumour-promoting inflammation.

However, the primary localization of the tumour is not the only aspect of the complexity of cancer disease, but it is necessary to consider the secondary localization. According to the modern theory regarding metastatic dissemination, the process occurs for interaction between disseminated cancer cells (DCC) and the engrafting site microenvironment[3]. The pathophysiological equilibrium is divided into cellular, angiogenic, and immune-mediated dormancy with this relationship being crucial for the metastasis cascade[4-6]. These processes should be considered as new potential targets in cancer therapy despite the fact that DCCs, and therefore metastasis, are not yet considered a hallmark of cancer[4].

Several possible interactions can occur between the immune system and tumour: elimination, equilibrium, tumour escape and growth, and increase in tumour-promoting immune cell populations. Immunotherapy can perturb this relationship in a tumour-rejecting sense, both in primary and secondary localization[7]. Immuno-oncology drugs act on the microenvironment of the tumour by modulating and enhancing the immune system response against malignancy[7,8]. A therapeutic mainstay of modern immune-oncology operates by inhibiting the "immune checkpoint" and potentially up-regulating all three arms of the system: T cell, B cell, and innate immunity[9].

Interventional oncology (IO) is an emergent field in interventional radiology that can be considered as the fourth pillar of oncology (together with medical, surgical, and radiation oncology)[10]. IO has the unique capability to treat malignancy in a loco-regional fashion enabling curative (percutaneous ablation), disease stabilization (intra-arterial chemo/radioembolization), and palliative treatment (such as biliary drainage or nephrostomy)[11]. Percutaneous ablation techniques exploit physical and chemical properties (laser-induced thermotherapy, radiofrequency, microwaves, cryotherapy, and irreversible electroporation) of the cells to locally treat malignancy. On the other hand, intra-arterial embolization therapy combines nutrient deprivation and hypoxia with either chemotherapy or radiation administration[12-14]. Overall, the whole arsenal of IO acts by inducing necrosis and apoptosis, with interactions with the tumour's microenvironment potentially crucial for oncological outcomes[15].

Considering that the tumour's microenvironment is a pivotal target for both immuno-oncology and interventional-oncology, the interactions between these two anti-tumour weapons should be investigated to understand their synergy[15]. In fact, immuno-oncology may regulate the immune system which is stimulated by interventional-oncology procedures. Substantial efforts have been directed to understand which technique combinations are the best for specific tumours. Yet, few articles take into account the administration timeline[16].

This article summarizes the latest evidence-reported literature and experience-based perceptions regarding the interaction and the synergy between both percutaneous and intra-arterial treatment with immune checkpoint drugs modulator.

Percutaneous Treatment and Immuno-Oncology

According to respective guidelines, percutaneous interventional oncologic approaches are considered the possible therapeutic strategies to treat primary and secondary tumours in several different cancers, particularly liver, bone, kidney,

and lung[17-20]. Both physical and chemical forces have been used for ablation, with the common goal to achieve loco-regional tumour eradication while preserving the surrounding healthy parenchyma[21]. The effect of all these energy sources is the necrosis of the tumour core and induced-apoptosis of the adjacent peripheral area[15]. From an immunological point of view, the necrotic tissue enhances the immune response, while apoptotic cells downregulate the system[22]. The necrosis induced by the percutaneous technique increases: the antigen presentation by dendritic cells, cytokines level, the CTLA-4 cascade, and the activation of the T-cell response[22,23]. This interaction leads to a dual effect: to improve local eradication and generate a remote, more systemic (i.e., Abscopal) effect[15,22,24,25].

Radiofrequency Ablation (RFA)

Thermal insult induces coagulation necrosis in the tissue target[26-27]. Mizukoshi et al[28] highlighted that there was a significant ($p<0.05$) increase of progression-free survival (PFS) at 25 months in hepatocellular carcinoma (HCC) patients with augmented level of tumour associated antigen (TAA)-specific T cells detected by IFN-γ ELISPOT assays after liver RFA (hazard ratio 4.054 [1.203-13.664]). Likewise, in a VX-2 rabbit liver cancer model, the combination of RFA and CpG B (a factor that stimulates innate immunity) increased the survival and the presence of activating lymphocyte compared with either RFA or CpG B alone[29]. In addition, Schneider et al[30] demonstrated a surge of $CD4^+$ and $CD8^+$ lymphocytes in the peripheral area of the ablation in non-small cell lung cancer (NSCLC) and intensification of pro-inflammatory cytokines. Moreover, Greten et al[31] combined RFA, cryoablation, and/or trans arterial chemoembolization (TACE) with tremelimumab (an anti-CTLA-4 checkpoint inhibitor) to treat patients with HCC experiencing continued progression while on sorafenib – anti-angiogenic – therapy. These authors showed different overall median survival rates of 9.2 months (95% CI 6.6-11.2), 15.0 months (95% CI 10.5-19.5), 13.8 months (95% CI 10.2-17.4), respectively, with few collateral effects (mostly pruritus and rash). Although the mechanism is incompletely understood, RFA has induced the abscopal effect by inducing necrosis, resulting in the increased presentation of tumour's antigens by dendritic cells[32]. In a colon-cancer murine model, the combination of RFA with a vaccine encoding CEA has produced regression of distal metastasis with a significant increase of CEA specific T $CD4^+$ compared with RFA or vaccine alone ($p<0.0001$; $p=0.0003$, respectively)[33]. However, the Abscopal effect determined by the RFA alone is weak, insufficient, or even occasionally counterproductive[29]. In fact, the dendritic cells need to receive maturation factors after the antigen presentation to avoid achieving an immunologically tolerogenic state. Moreover, in breast cancer induced in rat, RFA alone also stimulates hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF), which can be blocked by deactivating the HGF pathway (using PHA-665752) and using VEGF inhibitor (semaxanib)[34]. The stimulation of HGF and VEGF, without immunotherapy, resulted in increased cell replication (evaluated by Ki-67) and microvascular density in distant tumours[34]. Thus, this opposite systemic tumorigenic effect of RFA may explain the lower disease free-survival rate (31.7% *vs.* 61.1%) and the higher new intrahepatic tumour rate (62.7% *vs.* 36.6%) at 5 years of ablated HCC comparing with surgical resection. In addition, an incomplete radiofrequency ablation enhances HCC angiogenesis and progression in non-small cell lung cancer[31]. Thus, a further research is required to best determine how to achieve the desired immunogenic/abscopal effects in favour of the unwanted pro-tumorigenic phenomenon.

Cryoablation

Cryoablation induces coagulation necrosis of the tissue target due to endothelial damage by cycles of freezing and thawing that result in edema and inflammation[35]. While the central area of the ablation is comprised of necrotic tissue, the peripheral boundary, which is the critical zone for the outcome, is largely composed of apoptotic cells[36]. Of note, Takahashi et al[25] demonstrated in B16 melanoma cells that the optimal immune response was achieved by two cycles of freeze/thaw that coagulate only 73% of the target area. In another melanoma model, the combination of cryoablation and drugs anti-CTLA-4 increased the percentage of circulating T $CD8^+$ activated against malignancies[29]. In addition, it is important to stress that the efficiency of the dendritic cells was enhanced by cryoablation compared with both control and RFA[29,37]. Furthermore, still in another melanoma model, de Brok et al[37] demonstrated that the combination of cryoablation and CpG B induced the regression of the existing secondary tumours in 40% of treated mice.

Moreover, in a prostate cancer mouse model, the synergy between cryoablation and Anti-CTLA-4 slowed down the metastatic growth. In metastatic liver cancer patients, Niu et al[38] found that the median overall survival was significantly increased by the combination of cryoablation and immunotherapy, compared with cryoablation or immunotherapy alone[32] *vs.* 17.5 *vs.* 3 months; $p<0.05$). It is mandatory to underline that a recent literature suggests that the immunostimulatory response induced by cryoablation has been noted as the most potent among ablative therapies, as evidenced by significantly higher post-ablative levels of serum interleukin-1 (IL-1), IL-6, NF-κβ, and tumour necrosis factor-α (TNF-α)[37].

Microwave (MW), High Focal Ultrasound (HIFU), Laser-induced thermotherapy (LiTT), and irreversible electroporation (IRE)

Less evidence can be found in the literature regarding other ablation techniques. Regardless, Chen et al[39] showed in a hepatoma murine model that the combination of MW and GM-CSF significantly increased the survivor free tumour and decreased the tumour volume. Moreover, the combination of microwave and immunotherapies increased the free survival rates in patients with HCC, even if not significant[40].

HIFU has been used for primary and secondary malignancy of breast, soft tissue, bone, pancreas, kidney, and liver. HIFU can induce cytokine release and stress response with an augmented CD4+/CD8+ ratio. However, both MW and HIFU appear to be less immunogenic compared with RFA and cryoablation[41].

LiTT has been reported to increase the level of cytokines (IL-6, TNFRI and CRP level) in liver malignancy[42]. Moreover, Vogl et al[43] highlighted that the levels of $CD3^+$, $CD4^+$, and CD8+ before and after LiTT were increased (12.73 ± 4.83 *vs.* 92.09 ± 12.04; 4.36 ± 3.32 *vs.* 42.92 ± 16.68; 3.64 ± 1.77 *vs.* 47.54 ± 15.68; $p<0.05$) with augmented cytotoxic effects (RLU = 1493 ± 1954.68 *vs.* 7260 ± 3929.76; $p<0.001$).

In an HCC murine model, Bulvik et al[44] demonstrated greater lymphocyte infiltration and tumour resorption for IRE compared to RFA. Moreover, Lin et al[45] demonstrated in III/IV stage pancreas tumour, an increased level of progression-free survival and overall survival when combining IRE with allogeneic natural killer cell immunotherapy, compared with IRE alone. This finding was confirmed by Alnagger et al[46] in metastatic liver patients (IV stage) with an augmented overall survival. Furthermore, Vivas et al[47] showed that the administration of the immunogenic adjuvant (Poly-ICLC) before IRE was able to increase the immunogenic response and to reduce tumour growth in a VX2 model compared with IRE or Poly-ICLC alone (40%, $p<0.05$).

Intra-Arterial Treatment and Immuno-Oncology

Intra-arterial therapies for hepatocellular carcinoma are usually reserved for patients unfit for surgical or percutaneous approach[48,49]. Despite the palliative nature of such approach, there is much interest (as to) about how to potentiate its clinical results, especially in the setting of the presence of detrimental factors to achieve complete success rates (e.g.: advanced stage; tumour greater than 5 cm; multinodularity; poor post-procedural radiological response and inflammatory markers; post-procedural elevated serum AFP >20 ng/mL; VEGF levels above 44pg/dL)[50-53]. In fact, while inducing a direct necrosis due to anoxia induced by embolization, TACE significantly promotes angiogenesis, leading to the upregulation of angiogenic factors such as VEGF[51]. The signup regulation of multiple angiogenesis factors after intra-arterial treatments was also demonstrated by Ronald et al[54]. Specifically, it was demonstrated that elevated VCAM-1 and osteopontin levels allow a sustained upregulation, whereas IL-6 and osteopontin were also significantly correlated with radiologic response. Yet, Liu et al[51] combining TACE + sorafenib (molecule inhibitor of angiogenesis) aiming to counteract the paradoxical TACE angiogenic effect, failed to demonstrate a benefit in the setting tumours greater than 5 cm in diameter, indeed those tumours are known to have a worse outcome. Finally, sorafenib and the alternative molecules such as regorafenib (a multikinase inhibitor, targeting the VEGFR), bevacizumab (angiogenesis inhibiting monoclonal antibody directed at VEGF) as a stand-alone treatment failed to significantly ameliorate the overall patient survival[55-57]. Moreover, doxorubicin (the most common drug administrated in TACE) has been shown to induce immunogenic cell death and TAA. In particular, it has been shown that TAA-induced by TACE is associated with an increase in patient survival.

Over the last years, to overcome the limits of these scenarios, immunotherapy has gained prominence and is currently investigated as both stand-alone treatment and in combination with

trans-arterial therapies. To date, the major field of application has been the immune checkpoint blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1)[58].

The potential proof of concept trial for the use of CTLA antibodies in HCC investigated tremelimumab as a stand-alone treatment in a phase 1 trial. In detail, Sangro et al[59] demonstrated an objective response of 17% and a disease stabilization in 76% of patients with a median survival of 8 months in 21 patients with advanced HCC. Tremelimumab was administered every 90 days at a dose of 15 mg/kg intravenously until progression or intolerable toxicity. To date, no study is reported in combination with TACE.

With regard to PD-1 antibodies, the pivotal data leading to the approval of the drug came from the phase I/II CheckMate-040 trial (NCT01658878). In this study nivolumab was given as monotherapy. The objective response rate was 20% in patients treated in the expansion cohort and 15% in the dose-escalation phase, with a median overall survival of 13 months[60].

To date, multiple trials are running on the combination of these novel technologies with locoregional therapy treatment, including at least one trial in which radioembolization has been used (Table I).

Future Perspectives

Locoregional ablative therapies are minimally invasive procedures with an established role for the management of primary and secondary hepatic tumours. On the other hand, as a new therapeutic approach for malignancies beyond traditional operations, like chemotherapy and radiotherapy, the immunotherapy has shown its efficacy in delaying the progression of the advanced tumours and protecting the postoperative patients against cancer relapse and metastasis.

Over the last years, there is a growing interest in combining immunotherapy with locoregional strategies, but few data are available to guide how these modalities should be combined. What has become clear is that both percutaneous and intra-arterial treatments cannot be considered solely as a locoregional therapy, given their potential and global systemic effects. Yet, the resultant inflammatory response, though currently limited and unpredictable, paves the way for an expanded role of these procedures as stimulant to the immune system. However, these therapies represent a two-edged sword, as the causes and the solutions to its potential oncogenic effects need to be further investigated. Moreover, we strongly need to optimize the timing and dosimetry of immunotherapy and locoregional treatments that will be crucial for the creation of the most robust response, which could pave the way to curative therapy. Immunotherapy in conjunction with locoregional treatments could enhance treatment response with a high tumour burden, as a result of mechanical and immunologic changes in the tumour microenvironment. In addition, it can provide a great potential for the prevention of post-treatment tumour recurrence to gener-

Table I. Ongoing trials.

Trial	Aim	Phase
NCT02821754	To investigate tremelimumab (CTLA-4 antibody) and durvalumab in patients with advanced HCC (either alone or with cryoablation, TACE or RFA)	I/II
NCT02854839	To evaluate the safety and efficacy of MG4101 (allogeneic natural killer cells) in patients with HCC after TACE	II
NCT01853618	To test the safety and effectiveness of tremelimumab with TACE or RFA for advanced liver cancer	I
NCT02856815	To evaluate the efficacy and safety of 'Immuncell-LC group' and 'non-treatment group' in patients undergone TACE for intermediate stage HCC	II
NCT03099564	To evaluate the efficacy and the safety of combining pembrolizumab with Yttrium-90 (Y90) radioembolization in subjects with poor prognosis (high risk) HCC not eligible for liver transplant or surgical resection with well compensated liver function	I
NCT03099564	To evaluate the efficacy and the safety of combining pembrolizumab with Yttrium-90 (Y90) radioembolization in subjects with poor prognosis (high risk) HCC not eligible for liver transplant or surgical resection with well compensated liver function	I

CTLA: Cytotoxic T lymphocyte-associated antigen; HCC: hepatocellular carcinoma; MG4101: allogeneic natural killer cell line; RFA: radiofrequency ablation; TACE: trans-arterial chemoembolization.

ate a durable and powerful antitumor immunity, thereby achieving optimal tumour control. Future studies are required to identify more specific immune targets, novel immune checkpoints, and oncolytic viruses. These targets will enhance the intensity of tumour-specific immune responses and avoid unnecessary off-tumour toxicities.

Conclusions

The prospect of manipulating and potentiating the immune system toward the rejection of established cancers as part of the standard care of patients is becoming closer to reality, even if more data are still required to further verify the efficacy of this approach. The increasing number of available therapies may offer the opportunity to better tailor the treatment to patients according to the etiology, pathology, and biological tumoral features, as well as the physical performance status and the remaining liver function of patients. Overall, further studies combining immuno-oncology and interventional-oncologic techniques will most likely result in a paradigm shift, definitively changing the current conventional treatment algorithms of hepatic and future potential tumour therapy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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