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INVITED COMMENTARY

New generation cancer therapy: right direction for sure with some uncertainty

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The recent case report by Zacharakis et al. highlights the overwhelming effectiveness of sophisticated cancer immunotherapy along with immune checkpoint inhibitors [1]. The use of this logical approach helped a patient recover completely from advanced breast cancer, as planned by the researchers. This is one of the most famous case reports to date, signifying the landmark triumph of modern anti-cancer immunotherapy. Cancer immunotherapy was theoretically introduced in the early 1980s or even earlier. However, because of their limited clinical effectiveness, the first-generation cancer immunotherapy did not prevail in the clinical settings. Conversely, the advancement in the understanding of the mechanism of T cell activation has further enabled the development of immune checkpoint inhibitory drugs. Notably, anti-CTLA-4 antibody (ipilimumab) and anti-PD-1 antibodies (pembrolizumab and nivolumab) are already approved for the treatment of various solid tumors. For the treatment of hepatocellular carcinoma (HCC), several of these immune checkpoint inhibitors have been investigated [2–4]. The results of these inhibitors are extremely promising even when used in monotherapy. These inhibitors could be used as either first-line or second-line treatment for advanced HCC, although their final efficacies have not been clearly defined yet except for nivolumab [4]. Microsatellite instability (MSI) high or mismatch repair (MMR) deficiency could be possible biomarkers for cancer immunotherapy, especially for pembrolizumab as proved in colorectal cancers; however so far, they have not been established as treatment surrogate markers. Some of the patients treated using this inhibitor therapy exhibited a durable response (so-called CR) after administration of the immune checkpoint inhibitors. In the Kaplan–Meier curve of overall survival in each trial, the last portion of the curve corresponds to a horizontal flat, which may result from the complete remission of the malignancy [2]. This raises a question of how we can observe these remarkable successes with HCC. There are several probable means. First, historically, albeit rarely, cases of spontaneous regression of HCCs have been constantly reported. Second, the liver itself is an immunological organ in nature. However, it is also the first-line barrier for exogenous infiltrates after the mucosal barrier in the gut. The abundant immunological cells, including Kupffer cells and NK cells, behave as restless guards of hepatic sinusoids in this situation. Particularly, NK cells act as the primary tumor-eliminating cells even before clinically apparent solid tumor develops. In collaboration with the NK cells and T cells, the patient can maintain anti-tumor homeostasis. Another advantage of the liver in spontaneous regression is that the liver is rich in blood supply; therefore, immune cells can easily migrate to the liver. Indeed, the use of tumor-associated antigen-specific CD8-positive T cells is a potentially promising approach to treat HCC by using this blood access [5].

Currently, the treatment algorithm and guidelines for HCC are available from international societies, including APASL [6]. Moreover, molecular-targeting drugs have been used as the standard-of-care treatment for HCC. Sorafenib was introduced to the clinical setting almost 10 years ago. After tremendous failure of other molecular-targeting drugs combating sorafenib, both regorafenib and lenvatinib were subsequently approved for the treatment of HCC for the first time for 10 years [7–9]. Moreover, as the second line treatment, both ramucirumab and cabozantinib demonstrated promising efficacy in clinical trials [10, 11]. Thus, we will have more treatment options for both first-line and second-line systemic treatment for HCC. However, the treatment of HCC in the advanced stage remains unsatisfactory. Especially, systemic chemotherapy for advanced HCC is extremely intensive and expensive; nonetheless, the overall survival is far from satisfactory [12].

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Thus, the breakthrough therapy for advanced HCC is much warranted in the future. The most promising and budding approach is the combination of immune checkpoint inhibitors and anti-VEGF inhibitors. The theoretical advantage of this combination is quite straightforward, i.e., once HCC cells are insulted by molecular-targeting drugs, their broken proteins may serve as tumor antigen to induce anti-tumor immunities, after which the combination of immune checkpoint inhibitors could block the limiting inhibitory effects of PD-1/PD-L1 signaling between T lymphocytes [13]. In fact, the initial results of phase 1b trial announced in the annual meeting of American Clinical Oncology this year state that the combination of pembrolizumab and lenvatinib resulted in a remarkable disease control rate (unpublished data). Currently, immunologists and oncologists are focused on maximizing the effect of immune checkpoint inhibitors and molecular-targeting drugs, such as anti-VEGF or multiple kinase inhibitors (MKIs) [14]. The novel non-coding RNA technique could accelerate the speed of drug development [14, 15]. Moreover, the effort to understand the hepatocarcinogenesis at the molecular level is believed to herald novel drug development [16, 17]. Overall, we are presently facing dramatic changes in the treatment paradigms of HCC.

However, there are still some unresolved issues. First, not all patients with HCC can benefit from the above-mentioned novel therapies. Probably, the ongoing combination therapies and others may still offer new treatment modalities that can decrease tumor mass or induce immunological triggers. Thus, we may still require surgery, locoregional ablation (e.g., radiofrequency ablation), or radiation (conventional or particle beam radiation) for this purpose (Fig. 1).

Another issue is that tumor immunity is not always constant among patients. In other words, the capability of activating tumor immunity differs from person to person. To solve this problem, the genetic modification of T cells is fast becoming a routine practice in certain countries. More specifically, chimeric antigen receptor therapy or CAR T has exhibited extraordinary treatment successes in hematopoietic malignancies [18]. However, this success is seemingly difficult to reproduce in solid tumors such as pancreas cancer [19].

Apart from this dramatic improvement of anti-tumor effects, the new generation therapies are extremely expensive. The cheapest molecular-targeting drugs were reported to cost more than 20,000 USD for a year. The immune checkpoint inhibitors are even more expensive than molecular-targeting drugs, costing approximately 13,000 USD per month [20]. The most recent CAR T was reported to cost 4,000,000 USD for a single treatment. Of course, the price of these novel therapies could be gradually fallen to affordable levels in future; however nonetheless, it is still questionable whether all the patients in every region or country would appreciate the benefit from these cutting-edge treatments.

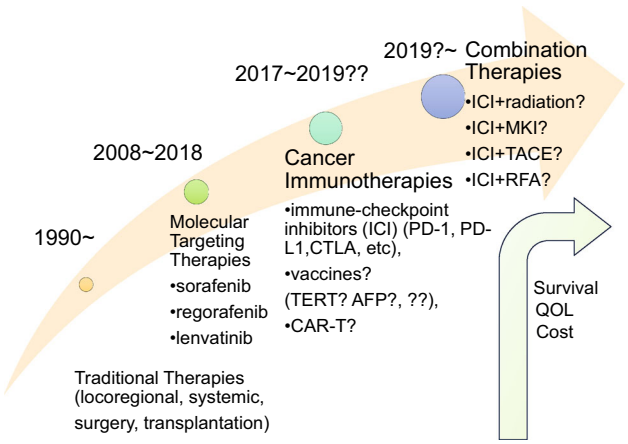

Fig. 1 The progress of treatment options for HCC. The standard of care for the treatment of HCC has changed by the emergence of new drugs. Both molecular-targeting drug and immune check inhibitors have brought dramatic changes. Further, combinations of these as well as traditional therapy are projected to improve the survival. Abbreviations: AFP: alpha feto-protein, CAR-T: chimeric antigen receptor T cell, ICI: immune checkpoint inhibitor, MKI: multiple kinase inhibitor, PD-1: programmed cell death 1, PD-L1: programmed cell death ligand 1, QOL: quality of life, RFA: radiofrequency ablation, TACE: transarterial chemoembolizaion, TERT: telomerase reverse transcriptase

Before detecting clinical malignancies, a single or few malignant cells circulate in our bloodstream [21]. Somatic mutation, which is the early event in the cellular malignant transformation, can precede a decade of clinical symptoms [22, 23]. Unfortunately, these premalignant events can increase with aging [23]. To establish cancer-free life, we need to find appropriate methods to correct genetic mutations that occur naturally in our life. For a long time now, we have called it "senescence" and have accepted this natural event. Fortunately and inevitably, sooner or later, we all will return to the soil as all the life on Earth do. It is therefore important to reflect on where we are heading and how much we can spend to prolong our lifetime.

Compliance with ethical standards

Conflict of interest The author does not have any potential conflict of interest regarding this article.

Human and/or animals rights This article is not applicable to document approval from IRB for research involving human participants and/or animals, and statement regarding obtaining informed consent.

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