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REVIEW ARTICLE

Why Adjuvant and Neoadjuvant Therapy Failed in HCC. Can the New Immunotherapy Be Expected to Be Better?

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Abstract

Introduction HCC remains a challenging disease with its unique characteristics and aggressive behavior. Although there are some curative-intent treatments such as liver transplantation and surgical resection, they themselves did not cure the patients with relatively high recurrence rates. Several modalities including local ablation methods like TACE or TARE, systemic treatments such as chemotherapy, tyrosine kinase inhibitors or antiviral therapies are tested in adjuvant or neoadjuvant setting, but none of them offered a survival benefit (except antiviral therapy in HBV-related HCC).

Conclusion After a decade of plateau in drug development, ICPIs came into podium with their different mechanism of action consistent with immunogenic nature of the disease and with high expectations, and ongoing trials will show if these agents can satisfy unmet demand in this area.

Keywords Adjuvant · Neoadjuvant · Immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the most common liver cancer worldwide, representing the third most common cancer in men and seventh in women [1, 2]. Despite the other common types of cancer, the incidence of HCC is increasing predominantly in men (fourfold higher in men than women), and this is valid for all major demographic groups and populations [3, 4]. For HCC, a major cause of cancer-related death, several locoregional and systemic treatments are available; however, only surgical resections, ablative therapies, and liver transplantation (LT) consist curative-intent options. Removing both the tumor and underlying liver disease LT seems the best option for this group of patients, but limited number of available organ donors all around the world and also limiting criteria which make the patient uneligible for transplantation are the main obstacles. Although the best results are restricted to small sized tumors, ablation is another reasonable option [5]. Given the factors mentioned above, surgical resection remains the most common curative treatment option for HCC patients. These patients absolutely have chronic liver disease (CLD) and some degree of cirrhosis, and as for all types of treatments recruited in HCC, the condition of the remnant liver determines the eligibility of surgical resections. On the other hand, recurrence rates after surgical resections is relatively high [6], and this is not only related with inadequate surgery (i.e., positive surgical margins) but also and frequently with developing de novo tumors in the course of the disease. Therefore, in order to improve the results of curative-intent options, especially of surgical resection, it is obvious that some additional treatment modalities are essential, and in this context, either neoadjuvant or adjuvant approaches must be taken into account.

Until now several types of treatments including transarterial chemoembolization (TACE), transarterial radioembolization (TARE) systemic treatments with chemotherapy, tyrosine kinase inhibitors, and immunotherapy are tested in both adjuvant and neoadjuvant settings, but unfortunately none of them is found related with improvement in overall survival and so not recommended in clinical practice by any guideline. In this review, the possible explanations of failure in (neo)adjuvant treatment options and also future projections and role of immunotherapy in this area which the demands are not met yet will be discussed.

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Neoadjuvant Treatment

Neoadjuvant treatments are commonly used in other solid tumors mainly to downstage the disease and make it resectable and predict the tumor response and so behavior preoperatively, but in HCC, the role of this approach is less well defined. HCC is unique with its aggressive behavior, frequent late diagnosis at advanced stage, and besides this, necessity of preserving limited liver capacity because of underlying liver disease to ensure surgical resection feasible makes the patients suitable candidates for neoadjuvant therapy. However, absence of effective options with high response rates to downstage the disease and concerns about hepatotoxicity related with treatment restricted its use until now.

Results of TACE in the neoadjuvant setting are controversial. Monden et al. [7] compared 71 patients treated with TACE preoperatively and 21 patients who underwent surgery without TACE and found that although there is no difference in overall survival, tumors treated with TACE are necrotized. In a retrospective analysis, Zhang et al. [8] reviewed results of 1457 patients of whom 120 treated with preoperative TACE and reported that 5-year disease-free survival was improved in patients treated with TACE. In addition, results were better for patients who underwent more than one course of TACE. In a meta-analysis including 32 randomized and non-randomized trials, there was no difference between patients treated with or without TACE preoperatively in terms of disease-free survival (DFS) and overall survival (OS). However, in patients with complete response to TACE, both DFS and OS were significantly improved [9].

In summary, neoadjuvant TACE did not reveal a survival benefit in HCC patients in general. But the results are better after sequential interventions and especially when complete response was observed. Besides the liver functions allowing multiple courses predictive factors determining complete responders is crucial to improve effectivity.

TARE is another option with similar results to TACE in respect to effectivity in neoadjuvant setting. Especially availability in patients with lobar portal vein thrombosis, TARE has some advantages over TACE including decreased toxicity and contralateral remnant liver hypertrophy without portal vein embolization [10–12]. Therefore, TARE comes step forward in patients requiring downstaging before surgery.

With its relatively poor toxicity profile and low objective response rates, systemic chemotherapy did not seem a good option in neoadjuvant setting in HCC and will not be discussed here. Tyrosine kinase inhibitors (TKIs), although showed effectivity in advanced disease and new generation agents, are being tested in combination with other molecules; none of them are tested in neoadjuvant treatment.

Adjuvant Treatment

The high recurrence rate after surgical resection prompted the attempts to develop effective postoperative (adjuvant) treatments. Despite other types of solid tumors, the goals of adjuvant therapy in HCC have different aspects: to eliminate residual microscopic disease in the classical concept of adjuvant treatment as in other solid tumors like breast and colon but also prevention of second primary HCC, called secondary chemoprevention. Recurrences in HCC usually occur in two different types as early and late. While early recurrences are tumor related, late recurrences which generally develop after 2 years of surgery are related with underlying disease associated with de novo tumors. Therefore, an effective adjuvant treatment in HCC must cover two patterns of recurrence.

Several strategies including antiviral therapies, TACE, radiation, and adoptive immunotherapy are tested in adjuvant setting, and only antiviral therapy in HBV-related HCC established survival benefit. All these mentioned methods will be out of the context of this review, and only systemic treatment options containing TKIs will be discussed in detail. STORM study [13] evaluated the efficacy of sorafenib, a multitarget TKI, as adjuvant treatment in resected HCC patients. It included 900 patients from 28 different countries, and after a median duration about 12 and a half month of treatment, no difference was observed in respect to relapse-free survival (RFS) between the two groups, and even sorafenib was associated with poor toxicity profile with four treatment-related deaths. Sorafenib besides inhibiting signal transduction pathways Raf-Ras and Mek-Erk mainly exhibits antitumoral activity by blocking VEGF. The authors mentioned when interpreting their results in adjuvant sorafenib and sunitinib in high-risk RCC trial [14] that VEGF blockage does not work in this setting. RCC resembles HCC in respect to its immunologic features. Therefore, a possible explanation for failure of adjuvant sorafenib in HCC may be this observation and is worth to note that neither TKIs nor MABs targeting VEGF did not show any effect in microscobic disease in any type of tumor. On the other hand as aforementioned, an effective agent in adjuvant setting in HCC must be capable in chemoprevention of second primary tumors. Given the class effects of multitarget TKIs, these agents are far from doing this. The latter factor is the major explanation for sorafenib failure in adjuvant setting.

Immune Checkpoint Inhibitors for Hepatocellular Carcinoma

Although importance of immune evasion in the development of HCC is well-known long before, lack of effective agents reversing cancer-related immunosuppression remained this domain undruggable till very recent time [15]. The liver has

a place at the junction between the host and continuous influx of gut nutrients, toxins, and metabolites. Besides its functions in maintaining host defense, the liver also plays a role in immune distinction between gut pathogens and self; however, in chronic liver inflammation, enhancement of gut permeability called "leaky gut" polarizes the liver microenvironment towards immunosuppression which has a role in tumorigenesis [16]. Orthotopic liver transplantation cures both cancer and cirrhosis but restricted to very few eligible patients [17]. Even in patients fulfilling Milan criteria, posttransplant recurrence rates reach 10% [18], and it is clear that OLT does not guarantee lifetime disease control at least in a proportion of HCC patients. Post-resection recurrence rates are up to 70%, and a 5-year survival ranging between 17 and 53% [19] declares the necessity for additional treatment modalities. Impaired antigen presentation through alterations in major histocompatibility complex (MHC) class I and aberrant expression of tumor neoantigens are the key mechanisms activating immune escape [20]. Immune checkpoint inhibitors (ICPIs) targeting either programmed cell death (PD) receptor on T cells or its ligands PDL-1 and PDL-2 on tumor cells and therefore activating immune surveillance have established significant antitumoral effect in several solid tumors including HCC in advanced stage with remarkable response rates and even complete responses. As pathologic complete response is a predictive factor for improved overall survival and given the high objective response rates and complete responses observed with these agents in advanced disease, it seems rationale to recruit ICPIs in the neoadjuvant treatment of HCC. Despite the optimistic prospects, because of the complexity of HCC, ICPIs must be used carefully in transplant candidates. One of the entities called event of clinical interest related with ICPI therapy is hepatotoxicity, and in a patient with a restricted liver function, this is an important issue that must be taken into account. Based on the data available, ideal candidates for neoadjuvant ICPIs are patients at high risk of post-OLT relapse, especially those with multifocal tumors, higher AFP levels, higher tumor volume, and poorer differentiation [21]. Although there is no phase 3 randomized clinical trial evaluating the effectivity of ICPIs in (neo)adjuvant setting in HCC results of interim analysis, phase II study evaluating perioperative nivolumab vs ipilimumab/nivolumab combo has yielded promising results with 29% complete response rate [22].

As discussed before, HCC has two different patterns of recurrence classified as early and late with a time threshold of 2 years [23]. Adjuvant ICPI by facilitating systemic clearance of microscobic residual disease seems effective in reducing early recurrence which actually is true disease reoccurrence but also with its chemopreventive effect, decreasing the incidence of de novo tumors. However, although the latter was less prominent, it is unique for ICPIs. Factors identifying optimal candidates for adjuvant ICPI include post-resection histopathologic high-risk features such as higher tumor burden, poor differentiation, multifocality, and most importantly microvascular invasion. Compared with neoadjuvant setting, optimal duration of treatment is an important issue in adjuvant ICPI treatment; increased toxicity observed when these agents are combined is also a major problem. Based on the data from preclinical studies and the expected mechanism of action, it seems rationale to use both neoadjuvant and adjuvant dosing instead of neoadjuvant or adjuvant immunotherapy alone [24]. As the allograft rejection rates are high, ICPIs should be avoided in patients who recurred after OLT [25]. There are ongoing phase 3 randomized trials [26–28] investigating safety and efficacy of ICPIs in the adjuvant treatment of HCC which are expected to be completed soon and will answer the questions in this area in the near future.

Conclusion

HCC is still a challenging disease with its unique characteristics. Multidisciplinary approach is essential in every stage of the disease. Although there are curative-intent treatment options such as resection and OLT, none of them offers lifetime disease control and necessitates additional treatments. Currently, there is no adjuvant or neoadjuvant treatment which is recommended in clinical practice as they did not reveal a clear survival benefit. This is not only just because of aggressive behavior and different recurrence pattern of the disease but also seems related with heterogeneity in study designs and patient selection. After a decade lasting stagnation in drug development ICPIs, reversing the immune-exhausted state in HCC shoved improvement in survival. Ongoing clinical trials besides determining optimal timing and which is the best combination will answer if these agents meet the all expectations.

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