Tamibarotene: a new hope for therapeutic efficacy in hepatocellular carcinoma patients

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Hepatocellular carcinoma (HCC) is one of the most common health threats worldwide. HCC is characterized by silent development and poor prognosis as well as 5-year survival rates of <5 %. The incidence and mortality rates of HCC are increasing in many countries, especially in Asian populations. The major risk factors for HCC development are hepatitis B and C viral infections, which contribute to 75 % of HCC cases. Other etiological factors, such as alcohol consumption, aflatoxin, obesity and diabetes, are also frequently observed in clinics [1, 2].

According to practice guidelines, treatment options include surgical resection, liver transplantation, percutaneous ablation, transarterial chemoembolization (TACE) and percutaneous ethanol injection, which are selected by hepatologists based on staging of primary HCC. In the early stage, surgical resection remains the most effective treatment with 40–70 % 5-year survival rates; however, only 10–20 % of the subjects with HCC are eligible for surgical resection because of poorly preserved liver function, portal vein invasion or extrahepatic spread [3]. TACE is recommended as the first-line treatment for HCC patients with intermediate stage disease and for downstaging tumors that exceed the criteria for transplantation [1]. One randomized trial evaluated the survival benefit with TACE and found that TACE-treated patients had a prolonged 2-year survival of 63 % compared with 27 % with only a supportive care [4]. Transarterial radioembolization (TARE) is based on the injection of radiolabeled particles through the hepatic artery into the in situ tumor and has

become another option for patients with intermediate-stage HCC in recent years [5]. A long-term follow-up check study demonstrated that TARE was well tolerated, with significantly lower rates of abdominal pain and elevated liver enzymes, but median survival was not significantly increased compared with TACE-treated patients [6]. Although improvements have been made in the treatment of HCC, the incidence and mortality rates of HCC are still increasing. This may be partially accounted for by the fact that most HCC patients are diagnosed at advanced stages [5]. Unfortunately, the available therapies for patients with advanced HCC are extremely limited. Sorafenib is a new multi-target drug that blocks tumor angiogenesis and proliferation by inhibiting the components of the Raf signaling pathway [7]. The safety and efficacy of sorafenib in the treatment of advanced HCC has been demonstrated in some recent clinical trials [8–11]. It improved the median survival time by ~3 months (the median for sorafenib was 10.7 months, while the median for the placebo group was 7.9 months) in patients with advanced HCC [10]. However, there is still a lack of significant treatment efficacy according to the response evaluation criteria in solid tumors (RECIST) [3]. In addition, the application of sorafenib was limited because of severe adverse events, including skin rash, hand-foot skin reactions, diarrhea and hypertension. Other potential treatments for advanced HCC, such as gene therapy and immunotherapy, are still under investigation and may be accepted as adjuvant therapies. Therefore, it is of great interest to develop more effective and practical therapeutic strategies for advanced HCC patients.

Tamibarotene (4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl] carbamoyl benzoic acid) is a synthetic retinoid that selectively binds to retinoic acid receptors [12]. Compared to all-trans retinoic acid, tamibarotene is chemically

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more stable and is a much more potent inducer of differentiation of promyelocytic leukemia cells. It was approved for treatment of relapsed and refractory acute promyelocytic leukemia in Japan in 2005 [13]. Tamibarotene has antiinflammatory and antiangiogenic properties that impact on tumor cell growth and autoimmune disorders [13]. It significantly inhibited proliferation of HCC cells in vitro, accompanied by upregulation of insulin-like growth factor-binding protein-3 [14]. It also inhibited VEGF-induced angiogenesis, promoted apoptosis, suppressed Th1 development and enhanced Th2 development of CD4 T cells [13, 15–17]. A recent study showed that tamibarotene inhibited Th17 differentiation in vitro and upregulated FoxP3 expression [18]. Retinoid inhibits the proliferation and the differentiation of several types of cancers by binding the retinoid receptor; therefore, tamibarotene might be a key candidate treatment for HCC.

However, the pharmacokinetics, efficacy and safety profiles of tamibarotene in the treatment of advanced HCC patients have not been reported. To address these issues, Kanai et al. [19] conducted an open-label phase I/II study that attempted to determine the maximum tolerated dose (MTD) and recommended dose (RD) for evaluation of the efficacy and safety profiles of tamibarotene in patients with advanced HCC. The authors performed the trial in 31 patients with histologically confirmed, measurable, unresectable HCC without systemic or local therapies. In the phase I study, 8 and 12 mg/day doses of tamibarotene were defined as the RD and MTD, respectively. No patient experienced dose-limiting toxicity at 8 mg/day. The encouraging result is that, in the phase II study, the total disease control rate was 32 % in 25 patients according to the RECIST criteria, including one patient who achieved partial response and seven who achieved stable disease. Drug-related serious adverse events were also reported: thrombosis in a limb vein, pulmonary artery and portal vein; interstitial lung disease and vomiting. Although the sample size in the clinical trial was small, this study found a new therapeutic use for a previously used drug in the treatment of HCC. Thus, this study provides initial evidence that tamibarotene could be considered as a novel alteration. More importantly, current findings allow further investigation of tamibarotene in a larger number of HCC patients.

Several concerns have been raised from these studies. First, important disease-related and drug efficacy-related biomarkers were not investigated in this study. These markers will help hepatologists to improve the management of HCC patients. Second, the mechanisms underlying the immunological response in patients receiving the therapy remain poorly understood. Given the close relationship between the action of tamibarotene and the immune response, further investigation of the immune

responses by which tamibarotene exerts its anti-HCC role should provide a deeper insight into the mechanisms and help develop a reasonable therapeutic regimen in clinics. Furthermore, it will help to determine whether tamibarotene influences liver injury, because hepatitis or liver cirrhosis may aggravate drug-related adverse events in the majority of enrolled patients who were infected with HBV or HCV in this study. Last but not the least, drug-related adverse events might limit its application. The drug-related adverse events of grade 3 or worse were observed in 45 % patients in this study [19], including thrombosis, AST increase, leukocyte decrease and c-GMP increase. Thrombosis as one of the serious adverse events is especially important for it may lead to exacerbation of patient's condition and an increase in the death rate. Although all patients who experienced thrombosis were successfully treated without clinical sequelae, the safety of tamibarotene in clinical use needs further evaluation. Also, the authors do not provide any information about the renal safety of tamibarotene, which again needs further evaluation in the future.

The results from this study indicate a promising treatment for HCC patients. Tamibarotene serves as a molecular targeted drug against HCC and, when used in combination with other antitumor drugs, the regimen may provide a multi-pathway blockade of HCC development and disease progression. In particular, it is necessary to evaluate tamibarotene as a first-line drug in advanced disease or as adjuvant therapy after surgical resection or locoregional therapies. In summary, future studies should be conducted in large prospective, randomized and controlled cohorts to validate the therapeutic efficacy and safety of tamibarotene in the treatment of HCC.

Conflict of interest None.

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