Hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and the third most common cause of cancer-related death worldwide. Furthermore, it is the fastest growing cause of cancer-related death globally.

Despite the implementation of screening programs to identify high-risk individuals, the majority of patients present with incurable disease.

Global epidemiological patterns vary depending on the prevalence of risk factors. Incidence rates are highest in East Asia in areas where hepatitis B and C are endemic. By contrast, obesity and metabolic syndrome in North America and Europe contribute to HCC being the fastest growing cause of cancer-related mortality in these regions.

The only chance to cure HCC is, of course, liver transplantation because this is the only way to cure the underlying disease.

Of course, resection is also a well-established tool to fight against HCC. In Innsbruck we also try to cure (or downstage) the patient with stereotactic radiofrequency ablation (sRFA). This is the reason why a paper is part of this HCC special issue. Locoregional therapy with transarterial chemoembolization (TACE) can lead to sustained disease control for intermediate stage HCC. However, only one third of patients present with disease suitable for these treatments [1].

For a very long time—a decade—in the palliative setting we were only able to offer sorafenib, a multitargeted tyrosine kinase inhibitor (TKI), to our patients. This drug showed improved median overall survival in patients with hepatocellular carcinoma.

After many years of disappointing results with chemotherapy, sorafenib was thought to herald a new era in HCC treatment with great optimism for molecular targeted therapies. Disappointingly, several negative first- and second-line phase III clinical trials ensued.

Since ASCO 2017 we can also treat our patients in the first line with lenvatinib. Now three years later, we have several lines (regorafenib, cabozantinib) and possibilities to treat our patients.

In hepatocellular carcinoma, an α -fetoprotein concentration higher than 400 ng/mL has been consistently associated with poor prognosis in several treatment settings and is a parameter that is included in several prognostic scoring systems.

α -Fetoprotein is a continuous variable. VEGF and VEGFR2-mediated signalling have important roles in angiogenesis and tumor growth, including in hepatocellular carcinoma. Increased α -fetoprotein concentrations have been associated with increased VEGFR expression and increased angiogenesis in hepatocellular carcinoma.

Ramucirumab is a human IgG1 monoclonal antibody that inhibits ligand activation of VEGFR2 (Vascular Endothelial Growth Factor). REACH was the first positive phase 3 trial done in a biomarker-selected patient population with hepatocellular carcinoma.

At the end of the day it is not easy to find the right therapy for the right patient [2].

Immunotherapies that inhibit the immune checkpoint interaction between programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) have shown substantial survival benefit in some patients with metastatic carcinomas of multiple tissue origins.

In general, immunotherapy failed in the treatment of gastrointestinal cancer—HCC is an exception. Very early the FDA approved nivolumab and pem-

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brolizumab for the therapy of HCC, unfortunately the phase III trials failed.

However, since the latest trial with atelizumab and bevacizumab we will have a first-line therapy with immunotherapy.

This month the FDA also approved the combination of nivolumab and ipilimumab for the treatment of HCC.

New questions also arise: should we give immunotherapy earlier (after resection or RFA)? What should we do when immunotherapy fails?

Nevertheless, there is a special group of patients who benefit more from TKIs—however we have to learn to select these patients [3].

The role of the microbiome in HCC is a very interesting tool to learn more about cancer [4].

I tried to find a collection of interesting topics for this special HCC issue—I hope you enjoy reading it, like I did.

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Conflict of interest A. Djanani declares that she has no competing interests.

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