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Artykuł przeglądowy / Review article

Management of hepatocellular carcinoma with novel immunotherapeutic agents and prospects for the future

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The most frequent type of primary liver cancer is hepatocellular carcinoma (HCC). Although HCC is not the most frequent cancer, it is characterized by high mortality – the 5-year survival rate is 6,9%. In recent decades there was only one molecule available in treatment (sorafenib). However, in the past few years there have been advances in treatment. Nowadays, new generation tyrosine kinase inhibitors, check point inhibitors and anti-angiogenesis drugs are available. All those studies were analyzed outcome in context of monotherapy or combined therapies. In this review we made an attempt to compare results from different studies. Even though, many studies are undergoing final stages of clinical trials, it seems that combined therapies should be the next step in treatment advances.

Key words: hepatocellular carcinoma, targeted therapy, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer. Globally, each year approximately 750,000 new cases are diagnosed, so it constitutes 7% of all neoplasms [1]. Although HCC is not the most frequent cancer, it is characterized by high mortality – the 5 year survival rate is only 6,9% [2]. Cirrhosis is the most important risk factor and is observed in 70–90% of patients [3].

Other factors are hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcoholism and aflatoxin B1. While the exposition of HBV infection in high incidence areas appears in at least 50% cases of HCC, HCV infection is more common in lower incidence HCC areas like Eastern Europe and North America [4, 5]. It has also been suggested that non-alcoholic fatty liver disease (NAFLD), occurring as a consequence of obesity and diabetes, can be the cause of an increasing number of HCC cases [6].

The most widely used staging system for HCC is the Barcelona Clinic Liver Cancer algorithm (fig. 1). Cancer is classified as an early-stage when patients have single liver tumors or as many as 3 nodules measuring 3 cm or less. They are treated by resection, transplantation or ablation. Intermediate-stage cancer concerns greater tumor burden confined to the liver without any symptoms and chemoembolization can be a beneficial treatment method. Advanced-stage cancer is when HCC symptoms are present and/or extrahepatic cancer and/or vascular invasion is/are diagnosed. The treatment of choice is the kinase inhibitor sorafenib [7].

The use of multi-kinase inhibitors and anti--angiogenic drugs in first-line treatment

Sorafenib has been used in HCC treatment for more than a decade. It is also used in renal cell carcinoma (RCC) and dif-
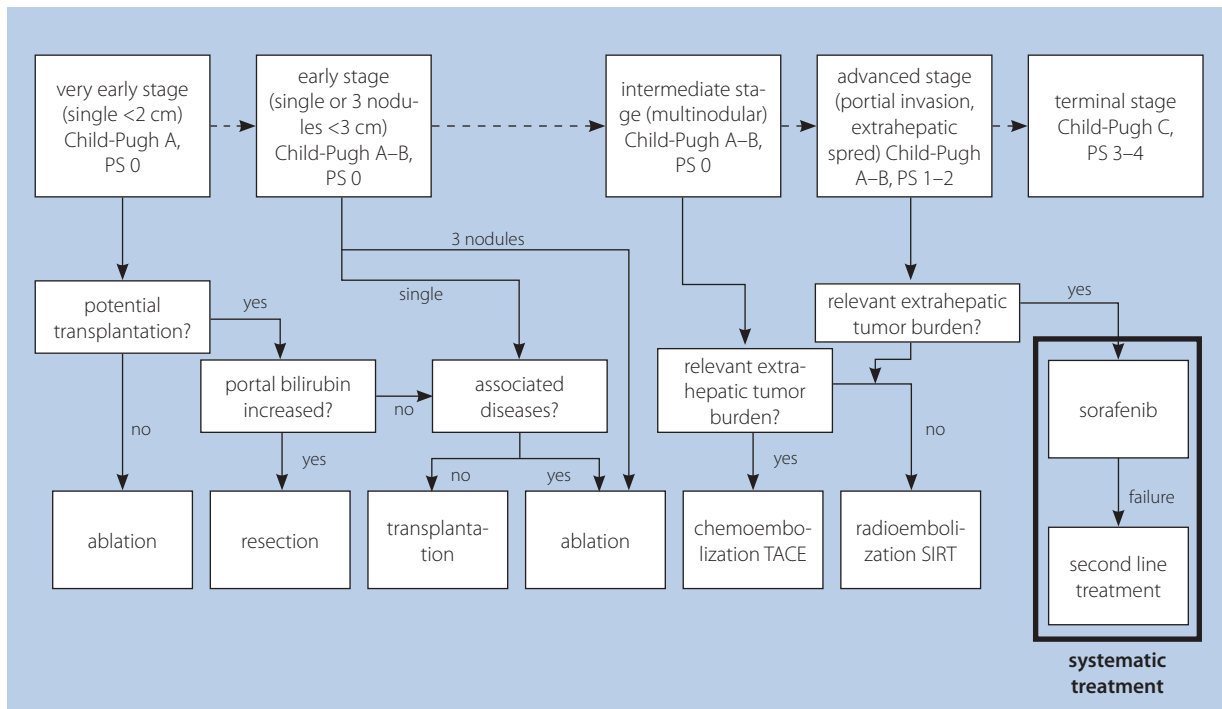
Figure 1. Barcelona Clinic Liver Cancer (BCLC) for HCC and available treatment strategies. In advanced stages, SIRT can be offered, if patients have no prognostically relevant tumor burden. Systemic therapy with sorafenib as a treatment by choice is recommended. In case of failure (clinical progression or intolerable toxicity), second-line treatment should be introduced [7]

ferentiated thyroid cancer (DTC) [8]. The mechanism of action is based on the inhibition of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor (PDGFR) angiogenesis through targeting the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway and receptor tyrosine kinases [9]. The role of sorafenib in HCC treatment is still being analyzed. The multicenter, double-blind, placebo-controlled trial of J.M. Llovet et al. focused on the differences in treatment of advanced HCC by sorafenib (at a dose of 400 mg twice daily) and placebo. They found that the median overall survival (OS) rate was 10.7 months in the sorafenib group, and 7.9 months in the placebo group with no significant difference in the median time in symptomatic progression. The median time in radiologic progression was 2.7 months longer in the sorafenib group [10]. A similar result was presented by J. Bruix et al. as they found that sorafenib improved median OS and the disease control rate (DCR) compared to the control group [11]. Another study showed that the efficacy of hepatic arterial infusion chemotherapy (HAIC) with cisplatin followed by sorafenib does not improve the survival rate in comparison with sorafenib alone; the median OS period in the HAIC group was 10 months and in the sorafenib group 15.2 months [12].

Lenvatinib is another drug used as a first-line treatment of HCC. Its mechanism is based on an inhibition of multiple receptor tyrosine kinases, including the vascular endothelial growth factor receptor 1 (VEGFR1), the vascular endothelial growth factor receptor 2 (VEGFR2) and the vascular endothelial growth factor receptor 3 (VEGFR3). It also impacts on angiogenesis, tumor growth and cancer progression by fibroblast growth factor receptors: FGFR1, FGFR2, FGFR3, FGFR4 and the platelet derived growth factor receptor alpha (PDGFRα) inhibition. Although there is no comprehensive comparison of both drugs in terms of OS, lenvatinib is considered as an alternative for sorafenib as there is significant improvement in OS (lenvatinib – 13.6 [95% CI: 12.1–14.9] months vs. sorafenib – 12.3 [95% CI: 0.4–13.9] months), longer progression-free survival (PFS) (7.4 [95% CI: 6.9–8.8] vs. 3.7 [95% CI: 3.6–4.6]) and time to progression (TTP) (8.9 [95% CI: 7.4–9.2] vs. 3.7 [95% CI: 3.6–5.4]) [13].

Second-line treatment

It is estimated that up to one-third of patients with advanced HCC qualify for second-line therapy. The necessity to change treatment options results from the failure of first-line therapeutics due to their high toxicity, disease progression or resistance to therapy of primary or adaptive mechanisms [14]. A study by Fung et al. on 730 Canadian patients showed that only 13.1% of patients would qualify for second-line treatment with regorafenib, cabozantinib or ramucirumab after using strict eligibility criteria (SEC). In turn, applying modified eligibility criteria (MEC) increased the size of the group under therapeutic treatment by more than half, reaching 31.7% [15]. Tivantinib, brivanib, and everolimus were considered promising candidates for inclusion as second-line systemic therapy for HCC. Unfortunately, in the third phase of clinical trials, they did not

show any significant benefit in terms of OS compared to the placebo [16–18].

Regorafenib

Until recently, patients treated with sorafenib who had not yet completed therapy due to progression or tolerance, could not count on any alternative form of systemic treatment. Bruix et al. (2016) published the results of their RESORCE study. They proved the effectiveness of using regorafenib as a second-line treatment in patients previously treated with sorafenib [19]. Regorafenib is an orally administered inhibitor of a set of multiple kinases responsible for angiogenesis (including vascular endothelial growth factor receptors 1–3 (VEGFR 1–3), tyrosine kinase with immunoglobulin-like and epidermal growth factor--like domains 2 (TIE2), fibroblast growth factor receptors 1–2 (FGFRs 1–2), the formation of metastases [VEGFR 2–3, PDGFR]) or the development of tumor immunity (colony-stimulating factor-1 receptor [CSF-1R]). These processes play a crucial role in the development of cancer and its progression [20]. In addition to second-line treatment, it is also used in therapy of refractory metastatic colorectal cancer (mCRC) and advanced gastrointestinal stromal tumors (GIST) [20, 21].

Cabozantinib

Cabozantinib is an orally administered tyrosine kinase inhibitor [TKI]. Its scope of action includes antagonistic effects against VEGFR 2, MET, KIT, RET, and AXL [22]. The MET tyrosine kinase receptor is the receptor for the hepatocyte growth factor (HGF). Their cooperation in a physiologically developing organism is important for processes such as the proper proliferation of cells or their motility [23]. However, in the case of HCC, melanoma, pancreatic, prostate, or ovarian tumors this mechanism is used by the tumor for its own benefit including growth and spread [22, 24]. HGF and MET antagonism, in turn, results in inhibition of tumor growth [25]. It is also believed that targeted MET and HGF therapies can overcome the barrier of HCC resistance to sorafenib treatment [26].

Based on the phase 3 results of the CELESTIAL study, cabozantinib was included in second-line standard of care for patients who had previously received sorafenib and had progressed. Abou-Alfa et al. conducted a randomized double-blinded trial including 707 patients with advanced HCC. The group was divided in a 2:1 ratio and the majority of patients received cabozantinib orally while the rest of the group received placebo. The initial dose was 60 mg and was decreased successively to 40 mg and 20 mg if necessary due to adverse events. The primary endpoint was OS while the secondary end points were PFS and objective ORR. Cabozantinib significantly increased the median of OS compared to placebo (respectively 10.2 months for cabozantinib and 8.0 months for placebo; HR 0.76; 95% CI: 0.63–0.92; p = 0.005). The median PFS was 5.2 months for cabozantinib and 1.9 months for placebo (HR 0.44; 95% CI: 0.36–0.52; p <0.001). Among the adverse events during therapy, the most frequent were palmar-plantar erythrodysesthesia (17% with cabozantinib and 0% in the placebo group), hypertension (16% and 2%, respectively), increased aspartate aminotransferase level (12% and 7%, respectively), fatigue (10% and 4%), and diarrhea (10% and 2% respectively) [27].

Ramucirumab

Ramucirumab is a recombinant human IgG1 monoclonal antibody that impairs angiogenesis which is essential for tumor development due to its VEGFR 2 antagonistic activity [28]. In a randomized double-blinded third phase REACH trial by Zhu et al., the efficacy of ramucirumab compared to a placebo was determined in patients with advanced HCC who had previously received sorafenib treatment. Initially there was no significant improvement in OS in ramucirumab-treated patients compared to placebo. Median OS of ramucirumab was 9.2 months vs 7.6 months with placebo administration (95% CI: 0.717–1.046; p = 0.1391) [29]. However, subsequent data analysis showed that ramucirumab significantly improved the OS score in patients with α-fetoprotein (AFP) ≥400 ng/mL [30]. The REACH II study included patients with advanced HCC (AFP values ≥ 400 ng/mL) and Child-Pugh class A liver disease treated only with sorafenib. 197 out of 292 subjects received ramucirumab therapy at a dose of 8 mg/kg intravenously every 14 days while 95 of them received placebo. The results showed that the median OS of ramucirumab treated patients was 8.5 months vs 7.3 months in the placebo group (HR of 0.71 [95% CI: 0.53–0.95]) while the PFS for ramucirumab was 2.8 months *vs*. 1.6 months for placebo (p < 0.0001). The most common adverse effects included hypertension (13% with ramucirumab *vs*. 5% with placebo), hyponatremia (6% *vs*. 0%, respectively), and increased aspartate aminotransferase (3% *vs*. 5%, respectively) [31].

Immunotherapeutic agents

One of the major problems in tumor management is their ability to escape from the immune system's range of action. Immuno-editing, which is a key aspect of immune evasion, is based on tumor-immune system interactions and Darwinian selection leading to decreased immunogenicity of the neoplastic cells. This in turn makes them invulnerable to the immune response. Attempts have been made to counteract those effects with immunotherapy. Experimental immunotherapy consists of two approaches: inducement of a new immune response and enhancement of the existing one [32]. Strategies of the *de novo* response stimulation include the usage of antigen targeting antibodies coupled with the immune cells, e.g. anti glypican 3 antibodies [33] and anti alpha-fetoprotein antibodies [34] conjugated with T cells or NK cells. Other examples are adoptive cell therapy using the chimeric antigen receptor expressing T cells (CAR-T cells) [35], cytokine induced killer cells (CIK cells) [36] or natural killer cells (NK cells) [37] and vaccine therapies with dendritic cell vaccines [38] or peptide vaccines [39].

The reinforcement of the existing immune response is based mainly on the pre-existing reactivity to neoplastic cells impeded by the microenvironmental components of the immune-edited tumor. One of the techniques aims at immune-inhibitory cytokines such as transforming growth factor beta (TGF-β) secreted by the neoplasm. The most relevant approach though, nowadays, is connected with the inhibition of immune checkpoints which is crucial in cancer immune evasion processes [40, 41].

Programmed death receptor 1 (PD1) is a surface protein expressed mainly by Tc lymphocytes but also by Th lymphocytes, Treg lymphocytes, B lymphocytes, NK cells, and some myeloid cells [32,33] which binds with its ligand PD-L1 (programmed cell death ligand 1). This triggers the metabolic cascade resulting in the inhibition of immune response by increasing the number and activity of Treg cells [42], inactivation of CD28 and downregulation of TCR in Tc cells [43] or their apoptosis [42, 44]. There are a number of clinical trials of PD1 inhibitors.

Nivolumab

Nivolumab is used for the treatment of patients with confirmed HCC and previously unsuccessfully treated with sorafenib. This indication was approved by the U.S. FDA in 2014 under accelerated approval due to its high efficacy and manageable safety profile demonstrated in CheckMate 040 open-label non--comparative phase ½ dose escalation and expansion trial in advanced HCC [45]. During both dose-escalation (n = 48) and dose-expansion (n = 214) phases (3 mg/kg), nivolumab showed acceptable tolerability. Although 46 of the dose-escalation patients (96%) discontinued treatment, 42 cases (88%) were due to disease progression. In the dose-expansion phase, the objective response (assessed using RECIST 1.1) was 20% (95% CI: 15–26) and in the dose-escalation phase it turned out to be 15% (95% CI: 6–28). The median OS rate was about two months longer (16.39 months) compared with sorafenib-treated patients (14.69 months). CheckMate 459, a phase III study on nivolumab in HCC (NCT02576509) is already in progress and results have not been published yet [46].

Camrelizumab

Camrelizumab is a humanized high-affinity IgG_4-kappa antibody PD-1 inhibitor used for the treatment of various neoplasms [47]. It has already received its first conditional approval in China for relapsed or refractory classical Hodgkin's lymphoma treatment in patients after receiving at least two systemic chemotherapies. Its safety and efficacy in patients with pretreated advanced HCC was evaluated in a multicenter open--label parallel-group and randomized phase 2 clinical trial [48]. The objective of the partial response evaluated by blinded independent central review (BICR) according to RECIST 1.1 was achieved in 32 of 217 patients (14,7%; 95% CI: 10.3–20.2). The 6-month OS probability was 74,4% (95% CI: 68–79.7), the 12-month OS was 55.9% (95% CI: 48.9–62.2) and the median

OS turned out to be 13.8 months (95% CI: 11.5–16.6). The rate of treatment-related adverse events was relatively low and manageable (grade 3 or 4 in 22% of patients). Phase III studies on camrelizumab in HCC (NCT03605706) and other malignancies such as non-smallll-cell lung carcinoma (NSCLC), gastric / oesophageal cancer, nasopharyngeal carcinoma are pending or ongoing [49].

Pembrolizumab

Pembrolizumab is a humanized monoclonal IgG4 kappa antibody that acts as a PD1 inhibitor indicated for a variety of neoplasms besides HCC, such as melanomas, NSCLCs, head and neck squamous cell carcinomas (HNSCCs), several type of lymphomas and others. The usage of pembrolizumab in HCC was approved by the FDA under accelerated approval based on tumor response rate and durability of the response shown in the KEYNOTE-240 study [50]. KEYNOTE-224 is a single-arm non-randomized multicenter open-label phase 2 trial [51] on 104 patients after disease progression, on or after sorafenib therapy and who had measurable disease and Child-Pugh class A liver impairment. 18 of the 104 patients displayed an objective response (17%; 95% CI: 11–26) including 1 complete and 17 partial responses. Treatment-related adverse events of grade 3 or worse were reported in 27 (26%) participants and grade 4 and grade 5 events affected 1 patient each. The results of further assessment in phase III trial KEYNOTE-240 were consistent with those of KEYNOTE-224, although OS and PFS measurements did not reach their co-primary endpoints and statistical significance per specified criteria. There are a number of trials studying other PD-1 inhibitors such as sintilimab (NCT03794440) [52], or tislelizumab (NCT03412773) [53]. Meta--analysis by Voutsadakis carried out with trials of selected PD-1 inhibitors showed no dissimilarities in effectiveness with other systemic therapies for HCC [54].

Durvalumab

Durvalumab is a monoclonal human immunoglobulin G1 kappa. The safety and efficacy of this PD-L1 inhibitor in relation to HCC was assessed in phase 1/2, a multicenter open-label study in patients with advanced solid tumors (NCT01693562). Grade 3–4 treatment-related adverse events occurred in 20% of patients and antitumor activity measured in ORR was calculated to be 10.3% (95% CI: 2.9–24.2) with a median OS of 13.2 months (95% CI: 6.3–21.1) [55].

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is another receptor that acts as an important immune checkpoint that through various mechanisms (e.g. inhibition of cytotoxic T lymphocytes, dendritic cells, activation of regulatory T cells etc. [56, 57]) contributes to the tumor immune evasion. The only CTLA4-inhibitor tested on HCC patients was tremelimumab – the results of the phase I trial displayed a partial response rate of 17.6% without major safety concerns [58]. HIMALAYA, a phase III study on tremelimumab in HCC (NCT03298451), is

already in progress as well [59]. Other immune checkpoints potentially relevant in HCC therapy (and oncology in general) are TGF-beta (e.g. NIS793 with PD-1 inhibitor spartalizumab – NCT02947165) [60], T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) (e.g. anti-TIM-3 and PD-1 – NCT03680508) [61] or lymphocyte activation gene 3 (LAG-3) (e.g. relatlimab and nivolumab – NCT01968109) [62].

Tremelimumab

As for other immunotherapeutics, with regards to worth mentioning is the combination of tremelimumab which is a human monoclonal antibody anti-CTLA-4 with ablative therapies that tend to induce peripheral immune responses [63–65]. According to a clinical trial by Duffy et al., in 19 patients who underwent tremelimumab administration and subtotal radiofrequency ablation or chemoablation, a confirmed partial response was observed in five subjects (26.3%; 95% CI: 9.1–51.2). Those patients received the infusion at two dose levels (3.5 and 10 mg/kg *i.v.*) given every 4 weeks for a total of 6 doses followed by 3-monthly administrations until the fulfillment of off-treatment criteria. In the study group, the median PFS was 7.4 months (95% CI: 4.7–19.4 months) and OS – 12.3 months (95% CI: 9.3–15.4 months) [66]. What is more, tremelimumab shows a significant activity in patients with HCC and chronic HCV infection and these conjectures were confirmed both in the study mentioned above [66], but also in the results of the clinical trial of Sangro et al. In the second case given, no ablative treatment was used and also the drug dose was different – 15 mg/kg *i.v.* every 90 days until progression or toxicity occurrence. Median TTP was 6.48 months (95% CI: 3.95–9.14) and a significant drop in the viral load provoked by the anti-HCV increased immune response was confirmed [58].

Combined therapies

Studies are underway to show the efficacy of a combination of anti-cancer drugs in the treatment of HCC. Combinations of anti-angiogenesis drugs with inhibitors of immune checkpoints (PD-1, PD-L1) used primarily in the treatment of lung cancer are being tested.

Atezolizumab and bevacizumab

In recent months, anti-PD-L1 activity has gained prominence in HCC treatment due to its anti-proliferative activity. The aim of the GO30140 study was to investigate the significance of atezolizumab (anti-PD-L1) alone and in combination with bevacizumab (anti-VEGF) in unresectable HCC. In a group of patients receiving the combined therapy of atezolizumab (1200 mg) and bevacizumab (15 mg/kg) with a median follow-up of 12.4 months, a confirmed objective response was observed in 37 (36%; 95% CI: 26–46) out of 104 patients; while for PFS, with a median follow-up of 6,6 months, it was 5.6 months (95% CI: 3·6–7·4). In the group receiving only atezolizumab in monotherapy, the median PFS was 3.4 months (1.9–5.2;

hazard ratio 0.55; 80% CI: 0.40–0.74; p = 0.011) [67]. Hack et al. compared also the HR for death – 0.58 (95% CI: 0.42–0.79; p < 0.001), OS at 12 months being 67.2% (95% CI: 61.3–73.1) *vs.* 54.6% (95% CI: 45.2–64.0) and PFS – 6.8 months (95% CI: 5.7–8.3) *vs.* 4.3 months (95% CI: 4.0–5.6); this was in atezolizumab plus bevacizumab and sorafenib-receiving groups with unresectable HCC with no prior systemic treatment. The results showed significantly better OS and PFS outcomes in atezolizumab + bevacizumab than sorafenib-receiving patients. According to the NCT04102098 study results, the PFS (in months) in the atezolizumab and bevacizumab group was even longer – 6.8 (5.7–8.3) [68].

Nivolumab and ipilimumab

As for other immunotherapeutic possibilities, there is much more to discover. In a Checkmate 040 randomized clinical trial in group A (obtaining nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks [4 doses] and then followed by nivolumab 240 mg every 2 weeks), the objective response rate (ORR) was 32% (95% CI: 20–47). In group B (obtaining nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks (4 doses)) ORR was 27% (95% CI: 15–41) and in group C (with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg administration every 6 weeks) – 29% (95% CI: 17–43). In groups B and C, the median duration of response was, respectively: 15.2 months (4.2–29.9+) and 21.7 months (2.8–32.7+) while in group A it was not reached until the end of the study period and this therapeutic pattern was approved in the US concerning the results and the good safety profile [69].

Tremelimumab and durvalumab

According to the results of the NCT02519348 clinical trial, tremelimumab (anti-CTLA-4 antibody) administered in a single dose of 300 mg combined with durvalumab (anti-PD-L1) in a dose of 1500 mg showed promising clinical activity and tolerance in patients with HCC with median OS of 18.73 months (10.78–27.27) and median ORR of 24% (95% CI: 14.9–35.3) with an acceptable safety profile. Tremelimumab-durvalumab combination remains evaluated in a phase III trial (HIMALAYA, NCT03298451) [70].

Ramucirumab and durvalumab

A 25-center study led by Bang [71] investigated the effectiveness of combined therapy with ramucirumab (IgG1, anti--VEGFR2) and durvalumab (IgG1, anti-PD-L1). The research subjects consisted of 28 patients diagnosed with HCC who had already been treated before. In the course of the study it was possible to obtain a partial tumor response to treatment in 3 out of 28 patients, of which two showed high PD-L1 expression. In contrast, 24 patients experienced treatment-related adverse events (TRAE). The most common were diarrhea (n = 8), fatigue (n = 6) and increased blood pressure (n = 4). Two patients died during the study due to complications: acute hepatitis

(TRAE) and acute respiratory distress syndrome (considered unrelated to treatment). It was assessed that the side effects of the combination of these two drugs do not go beyond the known complications of using each of them separately.

Pembrolizumab and lenvatinib

The effectiveness of the combination of pembrolizumab (anti-PD-1 antibodies) and lenvatinib (inhibitor of VEGFR1, VEGFR2 and VEGFR3 kinases) was investigated by Finn et al. [72]. A total of 100 patients received the combination of pembrolizumab and lenvatinib for an average of 7.5 months. Treatment efficacy was measured by the Modified Solid Tumor Response Criteria (mRECIST). The objective response rate (ORR) was 46.0% (95% CI: 36.0–56.3). The median duration of response (DOR) was 8.6 months (95% CI: 6.9 months to not estimable [NE]), the time to respond (TTR) – 1.9 months and PFS – 9.3 months (95% CI: 5.6–9.7 months). Median OS was 22 months (95% CI: 20.4 months to NE). The shrinkage of the tumor size was observed in 89% of the subjects. Almost all patients (99%) experienced side effects and the vast majority (95%) reported more than one. The most common ones were: hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%) and hypothyroidism (25%). 13 patients died during the course of study while 3 of the deaths were considered treatment-related. This study also did not find any side effects that would be different from those of the two drugs administered alone.

While in the above study the combination of pembrolizumab and lenvatinib is used as the first-line treatment, there are isolated reports of patients successfully treated with combination therapy after using sorafenib [73] or pembrolizumab as monotherapy [74]. Not to mention the promising results of studies testing the effectiveness of this treatment in the therapy of endometrial cancer [75, 76], stomach [77] or kidney [78].

Avelumab and axitinib

Another variant of combination therapy is the combination of avelumab (anti-PD-L1 immunoglobulin) and axitinib (a selective VEGFR kinase inhibitor). This therapy has been shown to be effective in the treatment of kidney cancer [79, 80].

A study by Masatoshi Kudo et al. [81] involved 22 HCC patients who were administered these two drugs. A reduction in tumor size was noted (according to mRECIST) in 16 patients and ORR was 31.8% (95% CI: 13.9–54.9). Side effects such as hypertension (50% of the respondents), hypothyroidism (31.8%), and hand-foot syndrome (22.7%) were observed.

Bevacizumab and erlotinib

An alternative version of combination therapy is the combination of a VEGFR inhibitor with a drug that inhibits EGFR tyrosine kinase. A study verifying the effectiveness of such treatment was carried out by M. B. Thomas et al. [82]. 90 subjects with advanced HCC were randomized into two groups and treated with a combination of bevacizumab (anti-VEGFR immuno-globulin) and erlotinib (n = 45) or sorafenib in monotherapy (n = 45). The median OS was identical for both treatments and reached 8.5 months (95% CI: 7.00–13.9 for bevacizumab+erlotinib vs. 95% CI: 5.69–12.2 for sorafenib). However, the duration of event free survival (EFS) favored the combination treatment (median – 4.37 months, 95% CI: 2.99–7.36) over monotherapy (median – 2.76 months, 95% CI: 1.84–4.80). Side effects were more frequent in the sorafenib group but also in this group the treatment was discontinued much more often due to the occurrence of serious complications.

The researchers, led by Liyun He, also came to similar conclusions. Their study included 342 patients with HCC and showed that bevacizumab and erlotinib therapy is as effective as sorafenib therapy and is associated with lower toxicity and better tolerance by patients [83]. However, this combined therapy does not show significant efficacy in second-line treatment [84] or treatment of residual disease [85]. Table I shows sorafenib and second-line treatment options.

Discussions

Multi-kinase inhibitors and anti-angiogenic drugs have been the most commonly applied therapeutic options in HCC treatment, including sorafenib, as the treatment by choice in advanced HCC. Unfortunately, these options present certain disadvantages. Their high toxicity and frequent cases of disease progression as well as possible therapy-tolerance development cause a high number of failures in HCC therapy.

Among the drugs that can be used in HCC therapy after unsuccessful first-line treatment are lenvatinib, regorafenib, and cabozantinib, while tivantinib, brivanib, and everolimus were rejected in this regard. Regorafenib has proven effectiveness after previous treatment with sorafenib failure due to progression or in tolerance. Cabozantinib, in turn, is effective to some degree in patients with tumor progression.

However, disadvantages and limitations of therapy cause a pressing need for development of innovative therapeutic strategies in HCC treatment. Among the others, some immunotherapeutic agents are highly prospective.

A relatively high number of clinical trials and some meta-analyzes involved PD-1 inhibitors of immune checkpoints (PD-1, PD-L1), including nivolumab, camrelizumab, pembrolizumab, durvalumab, and tremelimumab. Existing data concerning immunotherapy indicate various efficacy, but good tolerance of most of the agents and their generally acceptable safety profile. So far, clinical trials of nivolumab show a longer median survival rate than in sorafenib groups, making the immunotherapeutic agents both a possible alternative for sorafenib and a therapeutic option for second-line treatment. Camrelizumab research, in turn, indicates a median survival rate shorter compared to nivolumab, but without serious adverse effects during the therapy.

Another group of therapies involve combinations of anti-angiogenesis drugs with inhibitors of immune checkpoints

Table I. Overall response rate (ORR), overall survival (OS), time to progression (TTP) / progression-free survival (PFS) – sorafenib and second-line treatment options

	ORR	Median OS (months)	Median TTP / PFS (months)	Citation
sorafenib		10.7 (*vs.* 7.9 placebo)	2.7 (TTP)	[10, 11]
		10.0 (*vs.* 15.2 sorafenib + cisplatin)	3.9 (TTP)	[12]
cabozantinib		10.2 (*vs.* 8.0 placebo)	5.2 (PFS)	[27]
ramucirumab		9.2 (*vs.* 7.6 placebo)		[29]
		8.5 (*vs.* 7.3 placebo)	2.8 (PFS)	[31]
nivolumab		16.39 (*vs.* 15.69)		[45, 46]
camrelizumab		13.8		[49]
durvalumab		13.2		[55]
tremelimumab		12.3	7.4 (PFS)	[66]
atezolizumab + bevacizumab			5.6 (PFS)	[63]
atezolizumab + bevacizumab			6.8 (PFS)	[64]
nivolumab + ipilimumab	27–32%			[65]
tremelimumab + durvalumab	24%	18.73		[66]
pembrolizumab + lenvatinib	46%			[68]
avelumab + axitinib	31.8%			[77]
bevacizumab + erlotinib		8.5		[78]

effective against lung cancer. Among them nivolumab and ipilimumab, tremelimumab and durvalumab, as well as ramucirumab and durvalumab combinations are characterized by at least an acceptable safety profile and tolerance, while neither the combinations of pembrolizumab with lenvatinib, nor ramucirumab with durvalumab show other side effects than the drugs used alone. Some of the combinations, including avelumab and axitinib have proven efficacy in tumor size reduction, while, bevacizumab and erlotinib combine treatment present duration of EFS better than monotherapy.

Conclusions

The promising results of cancer immunotherapy may offer new hope for patients diagnosed with HCC. In those with advanced cancer, some immunotherapeutic agents may be a safe and an effective alternative for chemotherapy; alternatively they can constitute medications to be applied as a part of second-line treatment after the failure of previous options mentioned earlier. Particularly good results have already been achieved in combined therapy clinical trials.

A serious weakness of the studies existing so far is that they are often based on isolated reports or have other crucial limitations. Only a few immunotherapeutic agents have been already approved or are undergoing the final stages of clinical trials, while others remain highly experimental. Research projects aiming to gain more clinical data concerning the efficacy and safety of both drugs used in monotherapies or in combined therapies are already underway.

Conflict of interest: none declared

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