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Review article

Liver tumors

New targeted therapies used in the treatment of patients with advanced cholangiocarcinoma

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Cholangiocarcinoma (CC) is a rare yet exceptionally aggressive malignancy originating from the epithelium of the bile ducts. At the time of diagnosis, most patients are already in an advanced stage of the disease and qualify only for palliative treatment. Despite advances in oncological treatment, the prognosis for patients with advanced CC remains poor. Recently, several new molecularly targeted drugs have been developed, and their use may improve the prognosis for these patients. This article presents information about new molecules used in the treatment of patients with advanced CC: pemigatinib, futibatinib, and ivosidenib.

Keywords: cholangiocarcinoma, molecularly targeted therapy

Introduction

Cholangiocarcinoma (CC), also known as bile duct cancer, is a rare but exceptionally aggressive malignancy originating from the epithelium of the bile ducts. The incidence of CC in developed countries appears to be increasing [1]. The only method that offers a chance of curing the patient is surgical intervention; however, at the time of diagnosis, most patients are already ineligible for surgery. The standard first line chemotherapy for palliative treatment of bile duct cancer is gemcitabine combined with cisplatin [2]. Second-line treatment options are limited, with the FOLFOX regimen usually applied, which only slightly improves the prognosis when compared to symptomatic treatment alone. In patients with bile duct cancer, genomic profiling has led to the discovery of several potentially oncogenic alterations, including those in genes coding the fibroblast growth factor receptor (FGFR).

Fibroblast growth factor receptor alterations can lead to erratic FGFR signalling, driving oncogenesis through increased cell proliferation, migration, survival and invasion [3]. Fibroblast growth factor receptor 2 mutations are found almost only in intrahepatic bile duct cancer, occurring in less than 20% of patients [4–6]. Therefore, FGFR inhibitors appear promising for the treatment of bile duct cancer patients. Another potential therapeutic target in bile duct cancer is the mutated isocitrate dehydrogenase 1 (mIDH1). This article presents the results of studies on new molecularly targeted drugs used in the treatment of patients with advanced bile duct cancer.

Pemigatynib

Pemigatinib is a selective oral inhibitor of FGFR1-3. In a phase 2 study (FIGHT-202) [7], adult patients with advanced CC, who had disease progression after one or more lines of therapy and had FGFR2 mutations, or no FGF/FGFR alterations, received pemigatinib until progression of the disease or unacceptable treatment toxicity [7]. The primary study endpoint was the objective response rate (ORR) [7].

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Among 107 patients with FGFR2 mutations, 38 achieved an objective response. Three patients had a complete response (CR) and 35 had a partial response (PR) [7]. Disease control was achieved in 88 out of 107 patients. The median duration of response among responders was 7.5 months. The median progression-free survival (PFS) was 6.9 months [7]. Objective responses in patients with FGFR2 fusions or rearrangements were observed across all assessed subgroups, and the median PFS was generally similar.

The most common adverse event of any grade, regardless of causality, was hyperphosphatemia (reported in 88 out of 146 patients). Grade 3 or 4 adverse events occurred in 93 (64%) patients and included hyperphosphatemia, arthralgia, stomatitis, hyponatremia, abdominal pain and fatigue. Overall, there were 71 deaths, most commonly due to progression of the disease. No deaths related to pemigatynib were considered [7].

The introduction of FGFR inhibitors represents a significant advancement in treatment options. However, despite the presence of FGFR2 fusions or rearrangements, the duration of response and PFS were short for some patients. New research suggests that the short duration of response in these patients may be due to clonal evolution leading to acquired resistance mutations during FGFR inhibitor treatment [8]. Currently, pemigatinib is approved for previously treated patients with advanced CC with FGFR2 fusions/rearrangements in the USA (FDA) [9] and the European Union (EMEA).

Futibatinib

Futibatinib is a next-generation inhibitor of FGFR1–4. In a phase 2 study, the efficacy of the drug was evaluated in individuals with advanced CC with disease progression after previous systemic therapy and with FGFR2 alterations (fusions or rearrangements) [10]. Futibatinib was administered continuously to 103 patients at a dose of 20 mg orally. The primary endpoint of the study was the response to treatment (partial or complete), with secondary endpoints including duration of response, PFS and overall survival (OS).

Treatment response was observed in 43 patients [42%; 95% confidence interval (CI) 32–52) with an almost 10 month median duration response. After a median follow-up period of 17 months, the median PFS was 9 months, and the median OS was 21.7 months [10]. The most common grade 3 adverse events were hyperphosphatemia, elevated liver enzymes, stomatitis and fatigue. Treatment was discontinued due to adverse events in 2% of patients, and no treatment-related deaths were reported. Futibatinib has been approved by the FDA and EMEA for previously treated patients with advanced intrahepatic bile duct cancer with FGFR2 fusions or rearrangements.

Ivosidenib

In the ClarIDHy study [11], the efficacy and safety of ivosidenib, the first-in-class mIDH1 inhibitor, were evaluated. A total of 187 patients with previously treated advanced CC with an *IDH1* mutation were randomly assigned (2:1) to receive either ivosidenib or a placebo. The primary endpoint of the study was PFS, with secondary endpoints including OS, ORR, safety, quality of life. Upon disease progression, 70% of patients in the placebo group crossed over to the ivosidenib arm. The study demonstrated a significant benefit in PFS [hazard ratio (HR) = 0.37; $p < 0.0001$] and an ORR of 2.4% (3 PR) and 50.8% (63 stable disease) in the ivosidenib group compared to 0% and 27.9% (17 stable disease) in the placebo group. The drug was well-tolerated, with the most common adverse events being nausea, diarrhoea, fatigue, anaemia, and constipation. No treatment-related deaths were reported. Ivosidenib has been approved by the FDA and EMEA for previously treated patients with advanced CC harbouring the *IDH1* R132 mutation.

Summary

Cholangiocarcinoma remains a disease with a poor prognosis, and until recently, there were virtually no further treatment options after progression on cisplatin and gemcitabine chemotherapy. In recent years, three new targeted therapies have been registered for this indication: pemigatinib, futibatinib and ivosidenib. Compared to purely symptomatic treatment, these represent a significant advance; however, they have several limitations. It is important to remember that the use of these drugs is limited to patients with specific genetic alterations. Additionally, even when a response to treatment is achieved, the median time to disease progression is measured in months. The very significant cost of these therapies should also be noted. An undeniable advantage of these drugs is their relatively good tolerance and lack of negative impact on quality of life, which, considering their proven efficacy, makes them meet the fundamental goals of palliative treatment. Currently, none of the discussed drugs are reimbursed in Poland. In cases of disease progression after standard treatment and identification of a mutation justifying targeted therapy, individual applications must be submitted to the National Health Fund.

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Authors contributions

Aleksandra Śnios — writing, conceptualization.
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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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