

Review Article

Molecular Targeted Therapy for Biliary Tract Cancer- A Future Perspective

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INTRODUCTION

Bile duct cancer is subdivided according to the anatomic location of origin into intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer, or ampulla of Vater cancer. While biliary tract cancer is uncommon in Western countries, the incidence is relatively high in Asia, including Japan, and Latin America. However, in biliary tract cancers, the incidence of intrahepatic cholangiocarcinoma has been increasing even in the US, UK and Australia. In Japan, the estimated mortality of biliary tract cancer is 17,000 deaths annually.

While surgery remains the only potentially curative treatment, the curative resection rate remains low, at approximately 40% [1]. Furthermore, most patients develop recurrence even after curative surgery. Although unresectable and recurrent biliary tract cancer is treated by chemotherapy, no standard chemotherapy has been established. The ABC-02 trial, a randomized phase III study carried out in the UK [2] to compare gemcitabine alone with gemcitabine plus cisplatin (GC) in patients with unresectable or recurrent biliary tract cancer, demonstrated a statistically significantly higher overall survival in the GC arm as compared with that in the gemcitabine-alone arm. The BT22 study, a randomized controlled trial that compared GC therapy with gemcitabine alone, was conducted to confirm the efficacy and safety of GC therapy in Japanese patients; the trial yielded similar results to those of the ABC-02 study [3]. Thus, GC therapy has come to be recognized as the global standard for chemotherapy of unresectable biliary tract cancer.

In biliary tract cancer, nevertheless major advances in relation to the establishment of standard treatment, the prognosis in patients with biliary tract cancer is still poor. Each of the types of biliary tract cancer has characteristic features and the treatment strategy and prognosis also differ. It may be important to develop new chemotherapeutic regimens including molecular targeted agents, based on the biological features of the tumors.

BIOLOGIC FEATURES OF BILIARY TRACT CANCER

Various signal transduction pathways, including those involving the epidermal growth factor receptor (EGFR) and angiogenesis, that play important roles in the progression, proliferation, and metastasis of various cancers including biliary

tract cancer, have been identified.

EGFR consists of major 3 important signaling pathways, namely, the Ras/Raf/MAPK (Mitogen-Activated Protein Kinase) pathway, the phosphoinositide-3 kinase (PI3K)/Akt pathway, and the Jak/STAT pathway. Ras and/or Raf gene mutation are associated with diverse biologic functions, as well as have prognostic and predictive impact in various cancers such as colorectal cancer and non-small cell-lung cancer.

Biliary tract cancer includes various types of cancers, each with different molecular-biological characteristics. EGFR mutation is reported to be uncommon in biliary tract cancer [4-6]. The reported frequency of KRAS mutation varies from 13% to 54%, [5-10] with the detection rate of the mutation varying also by the tumor site. On the other hand, BRAF mutation is rare [5,6,9,11]. Until date, there has been no consensus on the molecular-biologic characteristics by tumor site in the bile duct.

Vascular endothelial growth factor (VEGF) is one of the most important factors involved in angiogenesis and is often over expressed in biliary tract cancer. VEGF and/or VEGF receptor (VEGFR) expressions, furthermore, have been shown to be associated with the risk of intrahepatic metastasis and the prognosis [12,13]. Therefore, molecular targeted agents targeting angiogenesis would be promising for the treatment of biliary tract cancer.

DEVELOPMENT OF MOLECULAR TARGETED THERAPIES AND FUTURE PERSPECTIVES

Molecular targeted agents have been investigated mainly as monotherapy or as components of gemcitabine-based combination regimens. Until date, among the various tyrosine kinase inhibitors investigated as monotherapy, most have failed to show promising efficacy in the early development stage. Phase II trials of monotherapy with sorafenib and sunitinib, which are multikinase inhibitors targeting VEGFR, platelet-derived growth factor receptor (PDGFR), and RAF or KIT (CD117), have been carried out. The response rate and time-to progression were relatively unsatisfactory, and the toxicity was also of concern [15-19]. On the other hand, selumetinib, which is an orally administered selective inhibitor of mitogen-activated ERK (extracellular signal-regulated kinase), or MEK, may be promising; the response rate is relatively high (12%), and the

Table 1: Clinical trials using molecular targeted agents for advanced biliary tract cancer.

Regimen	n	Response rate	Median PFS/TTP	Median OS	Author (year)
Erlotinib	42	7.1%	2.6 mo	7.5 mo	Philip [14]
Lapatinib	17	0%	1.8 mo	5.2 mo	Ramanathan [15]
Sorafenib	46	2.2%	2.3 mo	4.4 mo	Bengala [16]
Sorafenib	36	0%	3.0 mo	9.0 mo	El-Khoueiry [17]
Selumetinib	28	12%	3.7 mo	9.8 mo	Bekaii-Saab [18]
Sunitinib	56	8.9%	1.7 mo	4.8 mo	Yi [19]
Bevacizumab/erlotinib	53	12.2%	4.4 mo	9.9 mo	Lubner [20]
Gemcitabine/oxaliplatin/bevacizumab	35	40%	7.0 mo	12.7 mo	Zhu [21]
Gemcitabine/oxaliplatin/cetuximab	30	63.3%	8.8 mo	15.2 mo	Gruenberger [22]
Gemcitabine/oxaliplatin	74	29%	5.3 mo	12.4 mo	Malka [23]
Gemcitabine/oxaliplatin/cetuximab	76	23%	6.0 mo	11.0 mo	
Gemcitabine/oxaliplatin	133	16%	4.2 mo	9.5 mo	Lee [24]
Gemcitabine/oxaliplatin/erlotinib	135	30%	5.8 mo	9.5 mo	
Gemcitabine/cisplatin/sorafenib	39	-	6.5 mo	14.4 mo	Lee [25]

progression-free survival is 3.7 months (Table 1) [18]. Several MEK inhibitors are currently under investigation in early-phase clinical trials.

In regard to combination therapy, phase III trials of gemcitabine plus oxaliplatin (Gemox) with cetuximab or erlotinib, targeting EGFR, have been conducted; however, none has demonstrated survival benefit (Table 1) [20-25]. A phase II study of a combination of Gemox with bevacizumab yielded promising results, with a response rate of 40% and median overall survival of 12.7 months [21]. Chemotherapy combined with anti-angiogenesis agents may be warranted for further development of treatments for advanced biliary tract cancer.

There are two ways in which molecular targeted agents can be expected to be applied: administration in combination with standard chemotherapy regimens as first-line therapy, and monotherapy as second-line chemotherapy. GC therapy is established as first-line therapy, and administration of molecular targeted agents in combination with GC therapy may be tried as first-line therapy.

Patients who are refractory to first-line treatment are generally in a poorer general condition as compared to chemo-naïve patients. Therefore, less toxic treatments are required for second-line treatment, and monotherapy with molecular targeted agents should be investigated at first. To select appropriate subjects for a targeted agent, it is important to conduct early-phase clinical trials, so called proof-of-concept trial, to evaluate the efficacy and safety according to the biological characteristics.

Since biliary tract cancer is a relatively rare disease as compared to other gastrointestinal cancers, large-scale clinical trials of treatments for this cancer are difficult to conduct, and international collaboration is necessary for the establishment of new standard treatments.

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