

## 平成23年度大阪大学医学部医学科2年次9月学士編入学試験問題

## 英語

答は、すべて解答用紙に記入すること。

## 第3問

次の文章は肝細胞癌に対するソラフェニブの臨床試験成績を報告した論文の紹介記事である。これを読んで、以下の設問に答えよ。

Primary liver cancer is the fifth most common cancer worldwide and the third most common cause of death from cancer, resulting in (A)more than 600,000 deaths per year. The major risk factors for hepatocellular carcinoma are chronic hepatitis B or hepatitis C virus infection, alcoholic cirrhosis, and nonalcoholic steatohepatitis. Cancer probably develops in the cirrhotic liver through the induction of accelerated cycles of cell injury, death, and regeneration in an altered fibrotic and inflammatory microenvironment. Abnormal immortalized cell clones arise, and these cells develop genetic and epigenetic alterations that provide a survival and proliferative advantage, resulting in unconstrained proliferation, a key hallmark of cancer.

Early-stage hepatocellular carcinoma is amenable to potentially curative therapies; however, only about 30% of patients who present at most centers have early-stage disease. Liver cancer in an intermediate or advanced stage is particularly difficult to treat, for several reasons. Liver cancers typically retain active drug-metabolizing systems that contribute  an intrinsic resistance to chemotherapy drugs. Liver cancers also have enhanced expression of transporters of the multidrug resistance protein family, which mediate the export of chemotherapeutic drugs across the plasma membrane. Other factors also militate against response to therapy. Many drugs have intrinsic hepatotoxicity that may exacerbate the underlying liver disease. Leukopenia and thrombocytopenia that are caused by splenic sequestration from portal hypertension compromise therapy with agents that induce bone marrow suppression.

Until now there has been no proven medical therapy for advanced hepatocellular carcinoma. Therefore, randomized, placebo-controlled trials involving patients with advanced hepatocellular carcinoma are ethical and scientifically desirable. We have entered an era of targeted therapies for

human cancers that may be beneficial for both early-stage and advanced-stage tumors. Targeted therapies attack pathways that are critical for cancer <sup>(B)</sup>survival and progression and minimize off-target toxicity. Active and sustained efforts to elucidate the molecular pathogenesis of hepatocellular carcinomas have demonstrated the critical importance of activation of growth signaling pathways, including multiple receptor tyrosine kinase pathways, and inactivation of key tumor-suppressor genes. The highly vascular nature of hepatocellular carcinoma reflects profound activation of angiogenic signaling pathways, many of which are activated through receptor tyrosine kinases, resulting in stimulation of the Ras GTPase and Raf and mitogen-activated protein kinase molecules and their downstream targets, including the c-jun and c-fos transcriptional activators.

With the recently acquired elucidation of critical pathways for cancer survival and progression and the advent of new small-molecule and antibody-based therapies against cellular growth signaling and angiogenic pathways, investigators have looked with hope to the potential use of such targeted agents against this intractable cancer. A number of phase 1 and 2 studies have suggested that targeted agents that are administered singly or in combination may provide meaningful improvements in <sup>(C)</sup>survival for patients with hepatocellular carcinoma. Notably, these targeted agents do not induce the tumor involution and radiologic remission typical of the cytotoxic chemotherapies but rather result in disease stabilization and prolongation of survival, a new paradigm in cancer therapeutics.

In this issue of the Journal, Llovet et al. describe the positive results of a phase 3 study called the Sorafenib Hepatocarcinoma Assessment <sup>(D)</sup>Randomized Protocol (SHARP; ClinicalTrials.gov number, NCT00105443), which assessed the use of sorafenib in patients with unresectable hepatocellular carcinoma. <sup>(E)</sup>Sorafenib, a bisaryl urea, potently inhibits the serine-threonine kinase Raf-1 and both wild-type and V600E mutant variants of the Raf homologue B-Raf. In addition, sorafenib has substantial activity against multiple-receptor tyrosine kinases involved in tumor growth and angiogenesis, including vascular endothelial growth factor receptor (VEGFR) 1, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor  $\beta$ . In preclinical studies, sorafenib showed broad antitumor activity against colon, breast, and non-small-cell lung cancers and in liver xenograft models. The drug was approved b the treatment of advanced renal-cell carcinoma in 2005 and showed promising results in both phase 1 and 2 studies involving patients with hepatocellular carcinoma.

The investigators in the SHARP trial observed that in a population of patients with relatively preserved liver function (Child-Pugh class A cirrhosis), the use of sorafenib resulted in a modest but significant 3-month gain in survival over placebo. (F) This improvement in survival occurred despite a surprisingly limited partial response rate of 2%. Survival was extended because the drug was able to retard tumor progression. This represents an important first step in the application of targeted therapies for hepatocellular carcinoma. On the basis of these results, sorafenib was approved  b the treatment of advanced hepatocellular carcinoma by the European Agency for the Evaluation of Medicinal Products in October 2007 and by the Food and Drug Administration in November 2007.

We now look forward  c combination trials of sorafenib and similar agents with other treatment approaches and classes of agents to determine whether progressive improvement in survival can be achieved, as has occurred in the treatment of other solid tumors. For example, during the past 10 years, chemotherapy for colorectal cancer has advanced from single-agent therapy with fluorouracil to combination therapy with oxaliplatin, irinotecan, bevacizumab, cetuximab, or panitumumab. These advances have resulted in an increase  d the overall survival of patients with advanced colorectal cancer from 6 months with best supportive care to more than 2 years with the use of various combinations of active agents.

The advent of sorafenib now provides a benchmark against which other agents and combinations can be tested. In particular, given that (G) the SHARP study almost exclusively involved patients with Child-Pugh class A cirrhosis and relatively compensated liver disease, it will be important to determine the efficacy and side-effect profile of sorafenib in patients with Child-Pugh class B cirrhosis. Other important questions are whether the drug prevents disease recurrence after surgery or ablative therapies or extends survival in patients undergoing chemoembolization.

It will be important to carefully monitor adverse events associated  e sorafenib in postmarketing surveillance to ensure that no additional risks are identified in patients with liver cancer. Key side effects in patients with renal-cell carcinoma include a significant risk of hypertension and other cardiovascular complications. Sorafenib has also been implicated in the development of the reversible posterior leukoencephalopathy syndrome. Other important adverse effects include diarrhea, weight loss, rash, fatigue, and hand-foot skin reactions.

In summary, the SHARP trial sets a benchmark for a new era of targeted therapies in hepatocellular carcinoma. These results give hope for further advances in therapy during the exploration of the potential efficacy of sorafenib and other agents in combination with local or locoregional therapies.

A final, necessary concern that applies particularly to the era of targeted therapies for cancer is the issue of cost. The pharmacy price of sorafenib is approximately \$5,400 per month in the United States, 3,562 euro per month in France, \$1,400 per month in Korea, and \$7,300 per month in China. Even in industrial nations, the high cost of new drugs produces significant stresses on health-system budgets. As we have learned in recent years from the worldwide epidemic of the acquired immunodeficiency syndrome, there are substantial ethical implications in having effective therapies available for life-threatening diseases that are priced beyond the reach of the populations most in need of therapy. This is particularly applicable for liver cancer. Although the disease is the third most common cause of death from cancer worldwide, over half of the more than 600,000 deaths per year occur in China alone, and most of the remaining deaths occur in poor countries of sub-Saharan Africa. We therefore have another dilemma on hand – (H)that of having coals in Newcastle without the ability to distribute them through the countryside. This situation stresses the importance of worldwide public-private partnerships to enhance the research enterprise, bring new agents to market in a more cost-effective fashion, and provide effective therapies to suffering patients at costs that are within their reach.

#### 注釈

hepatocellular carcinoma, 肝細胞癌; hepatitis, 肝炎; cirrhosis, 肝硬変; leukopenia, 白血球減少; thrombocytopenia, 血小板減少; portal hypertension, 門脈圧亢進; bone marrow, 骨髄; renal-cell carcinoma, 腎細胞癌; Child-Pugh class, 肝硬変の進行度分類 Aは軽症、B, Cは重症である。; partial response, 抗癌剤の効果判定基準のひとつであり、腫瘍が30%以上退縮した場合をこのようによんでいる。腫瘍が消失した場合は complete response、腫瘍の30%未満の退縮、20%未満の増大を stable disease、20%以上の増大を progressive disease と分類する。

The New England Journal of Medicine, Vol. 359 No.4 (July 24, 2008) から抜粋

## 問1

下線部 A に示す年間死亡者数の中で、最も多い地域を次から選びなさい。

- ① 米国
- ② 日本
- ③ 中国
- ④ アフリカ

## 問2

下線 B と下線 C の survival の意味の違いを日本語で説明した下の文を完成させなさい。ただし、甲と乙にはそれぞれ日本語で3文字ずつ入るものとする。

B は  の生存、C は  の生存について述べている。

## 問3

SHARP 試験は sorafenib の有用性を科学的に検証するため、登録された患者を無作為に sorafenib 投与群とプラセボ（偽薬）投与群に割り付けている（下線 D）。このような試験はプラセボ投与群患者に不利益を与える可能性があるが、このような試験デザインが可能であった理由について説明している文を一つ抜き出さなさい。

## 問4

下線部 E に sorafenib という薬剤の作用機序が述べられている。このような性質をもつ薬剤の総称として適当な言葉を抜き出さなさい。

## 問5

下線部 F で著者は「驚いたことに」と述べているが、一方でこのことは必ずしも驚くべきではないという考え方がある。そのことを記した文を一つ抜き出さなさい。

## 問6

SHARP 試験の患者の登録が下線部 G のように行われた背景を考え、それを説明している最もふさわしい文を一つ抜き出さなさい。

問7

下線部 H は比喩表現である。具体的にどのようなことを述べようとしているのか日本語で簡単に説明しなさい。

問8

次の文章はこの紹介文の対象となった論文の要旨の結論部分を抜き出したものである。空欄に最もふさわしい単語を入れなさい。

In patients with  hepatocellular carcinoma, median survival and the time to radiologic progression were nearly 3 months  for patients treated with sorafenib than for those given placebo.

問9

空欄 a~e に最も適当な単語を挿入しなさい。