JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(12)1189–1191
doi:10.1093/jjco/hyq110
Advance Access Publication 14 July 2010

Clinical Trial Note

Randomized Phase II Study of Gemcitabine plus S-1 Combination Therapy vs. S-1 in Advanced Biliary Tract Cancer: Japan Clinical Oncology Group Study (JCOG0805)

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Received May 11, 2010; accepted June 1, 2010

A randomized Phase II selection design trial comparing gemcitabine plus S-1 combination therapy with S-1 monotherapy for chemo-naïve unresectable or recurrent biliary tract cancer patients was started in Japan. The aim of this trial is to evaluate the efficacy and safety of the two regimens and to determine which is more promising as a test arm regimen to be compared with the current standard regimen, gemcitabine plus cisplatin, in a subsequent Phase III trial. Patients with unresectable or recurrent biliary tract cancer are randomized to either gemcitabine plus S-1 combination therapy arm or S-1 monotherapy arm. A total of 100 patients will be accrued for this study from 18 institutions over 1 year. The primary endpoint is the proportion of 1-year overall survival, and the secondary endpoints are progression-free survival, response rate and adverse events.

Key words: iliary tract cancer – gemcitabine – S-1 – randomized Phase II selection design trial

INTRODUCTION

Biliary tract cancer consists of intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and ampulla of Vater cancer. In Japan, it is estimated that ~18 000 patients with biliary tract cancer die annually and it is the sixth leading cause of cancer death (about 5.6% of all deaths due to cancer) (1,2).

In biliary tract cancer, curative surgical resection offers the only chance for a cure; however, most patients are initially diagnosed with unresectable disease. Moreover, many patients who undergo curative surgery develop recurrence (3).

For unresectable or recurrent biliary tract cancer, systemic chemotherapy is recognized as a standard treatment and, globally, gemcitabine, platinum analogue and fluoropyrimidine are considered as the key drugs (3,4). Although gemcitabine alone was regarded as the standard regimen for the advanced biliary cancer until recently, gemcitabine plus cisplatin (GC) has become the new standard regimen on the basis of the results of the ABC-02 trial (5), in which the superiority of GC over gemcitabine alone was shown.

Gemcitabine plus S-1 combination therapy (GS) or S-1 monotherapy is another promising regimen for unresectable or recurrent biliary tract cancer. In a Phase II trial for biliary tract cancer, S-1 monotherapy showed a better response rate (35%) (6) than gemcitabine alone (17.5%) (7) with milder toxicity. GS also showed a better response (34%) than gemcitabine alone in a Phase II trial for biliary tract cancer (8), even though the former showed much more toxicity than the latter. Therefore, we regard both regimens as promising and

planned this randomized Phase II trial to determine which regimen is more promising as the test arm regimen in a subsequent Phase III trial, in which the test arm will be compared with the current standard regimen, gemcitabine plus cisplatin.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved this protocol in December 2008 and the study was initiated in February 2009. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000001685 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGESTS OF THE JCOG0805

Objectives

The aim of this study is to evaluate the safety and efficacy of the two regimens and to determine which regimen is more promising as the test arm regimen in a subsequent Phase III trial.

Study Setting

The study was a multi-institutional open-label randomized Phase II selection design trial.

Resources

This study is supported by Grants-in-Aid for Cancer Research (20S-3, 20S-6) Health and Labour Sciences Research Grant for Clinical Cancer Research (19–22), from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is the proportion of 1-year overall survival in all eligible patients. Overall survival is defined as days from randomization to death from any cause, and it is censored at the last follow-up day when the patient is alive. The secondary endpoints are progression-free survival, response rate and adverse events.

Progression-free survival is defined as days from randomization to disease progression or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of progression.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, patients are required to fulfill all of the following criteria.

(i) Clinically diagnosed with biliary tract cancer, which includes intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and ampulla of Vater cancer.
(ii) Recurrent or unresectable biliary tract cancer.
(iii) Histologically proven papillary adenocarcinoma, tubular adenocarcinoma, or adenosquamous carcinoma for extrahepatic cholangiocarcinoma, gallbladder cancer and ampulla of Vater cancer patients. Histologically proven adenocarcinoma for intrahepatic cholangiocarcinoma patients.
(iv) Without central nervous system metastasis.
(v) Without moderate or more severe ascites and pleural effusion.
(vi) No previous therapy against biliary tract cancer.
(vii) No previous chemotherapy or radiotherapy against any other malignancies.
(viii) ECOG performance status of 0 or 1.
(ix) Sufficient oral intake.
(x) Aged 20–79 years old.
(xi) Adequate organ functions.
(xii) Written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria.

(i) Simultaneous or metachronous (within 5 years) double cancers, with the exception of intramucosal tumor curable with local therapy.
(ii) Pregnant or lactating women or women of childbearing potential and men who want to get their partner pregnant.
(iii) Psychosis.
(iv) Requiring systemic steroid medication.
(v) Interstitial pneumonia or lung fibrosis.
(vi) Watery diarrhea.
(vii) Active bacterial or fungous infection.
(viii) Severe complication: heart failure, renal dysfunction, liver dysfunction, hemorrhagic peptic ulcer, paresis of intestine, ileus, uncontrollable diabetes mellitus etc.
(ix) Requiring the administration of flucytosine, phenytoin or warfarin potassium.
(x) Drug allergy for iodic drugs or gadolinium.

Randomization

After confirmation of fulfillment of the eligibility criteria, registration is made by telephone or fax to the JCOG Data Center. Patients are randomized in the JCOG Data Center by a minimization method balancing the arms with institution, primary tumor (gallbladder cancer/intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma or ampulla of Vater cancer) and clinical stage (II, III/IV or recurrent).

Treatment Methods

For the GS arm, 1000 mg/m^2 gemcitabine is infused on days 1 and 8, and 30 mg/m^2 S-1 is orally administered twice per day from days 1 to 14, repeated every 3 weeks.

For the S-1 monotherapy arm, 40 mg/m^2 S-1 is orally administered twice per day for 4 weeks, followed by a 2-week rest, repeated every 6 weeks.

Protocol treatments in both arms are continued until progression, unacceptable toxicity or patient refusal.

Follow-up

Enhanced abdominal computed tomography (CT)/magnetic resonance imaging, chest CT/X-rays and tumor markers (CEA and CA19-9) are evaluated at least every 6 weeks during the protocol treatment. Adverse events are evaluated at least every 2 weeks during the protocol treatment using CTCAE ver. 3.0.

Study Design and Statistical Analysis

This study is a randomized Phase II selection design trial (9) to evaluate which regimen, GS or S-1, is more promising for the test arm regimen for a subsequent Phase III trial. The regimen that shows the higher point estimate in terms of the proportion of 1-year survival will be considered to be more promising.

The frequency of toxicity is expected to be higher in GS than in S-1 monotherapy, but we expect that the frequency of severe toxicity will be almost equivalent. Therefore, we will select the more promising regimen on the basis of efficacy, namely, 1-year overall survival, as long as the levels of severe toxicity do not differ markedly between the two arms.

Sample size was determined as follows by Simon's selection design. We assumed that 1-year survival of one regimen is 30% and that of the other regimen is more than 40%. In this situation, the sample size ensuring at least 85% probability of correct selection of the more effective regimen is 98 patients, with 49 patients per arm. Considering the likelihood of some ineligible patients being enrolled, the total number of patients was set at 100.

Interim Analysis and Monitoring

We do not plan the interim analysis in this study. In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate the study progress and to improve the study quality.

Participating Institutions

The participating institutions (from north to south) are as follows: Sapporo-Kosei General Hospital, Tochigi Cancer Center, Jichi Medical University, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center Hospital, National Cancer Center Hospital, Kyorin University School of Medicine, Cancer Institute Hospital, Kanagawa Cancer Center, Yokohama City University Medical Center, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center and Kyushu University Hospital.

Acknowledgements

The authors thank Mr. Taro Shibata for statistical study design.

Conflict of interest statement

None declared.

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