Valle J et.al N Eng J Med 2010;362:1273-1281

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

切除不能胆道がん患者を対象とした，ゲムシタビン（商品名ジェムザール）単独投与群とゲムシタビンにシスプラチンを併用する群の治療効果を比較したランダム化比較試験結果

BACKGROUND

There is no established standard chemotherapy for patients with locally advanced or metastatic biliary tract cancer. We initially conducted a randomized, phase 2 study involving 86 patients to compare cisplatin plus gemcitabine with gemcitabine alone. After we found an improvement in progression-free survival, the trial was extended to the phase 3 trial reported here.

METHODS

We randomly assigned 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter on days 1 and 8, every 3 weeks for eight cycles) or gemcitabine alone (1000 mg per square meter on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary end point was overall survival.

RESULTS

After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin–gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001). The median progression-free survival was 8.0 months in the cisplatin–gemcitabine group and 5.0 months in the gemcitabine-only group (P<0.001). In addition, the rate of tumor control among patients in the cisplatin–gemcitabine group was significantly increased (81.4% vs. 71.8%, P=0.049). Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin–gemcitabine group; the number of neutropenia-associated infections was similar in the two groups.

CONCLUSIONS

As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine is an appropriate option for the treatment of patients with advanced biliary cancer. (ClinicalTrials.gov number, NCT00262769.)

治療法：

ゲムシタビン単独群(206 例)：ゲムシタビン 1000mg/m2 の 30 分点滴静注を day1，8，15 に，4 週毎 6 サイクル繰り返す。

シスプラチン併用群(204 例)：day1，8 にシスプラチン 25mg/m2 の 2 時間点滴後にゲムシタビン 1000mg/m2 の 30 分点滴静注を行い，3 週毎 8 サイクル繰り返す。

効果指標：

（主要評価項目）全生存期間

（副次的評価項目）無増悪生存期間，有害事象

結果：

1. 患者背景因子

両群に患者背景因子の偏りは認められない。

2. 治療状況

・計画治療　ゲムシタビン単独群(3 サイクル投与)：66.5%，シスプラチン併用群(4 サイクル)：73.5%

・腫瘍増悪のため治療中止　ゲムシタビン単独群：49 例，シスプラチン併用群：26 例，P=0.004

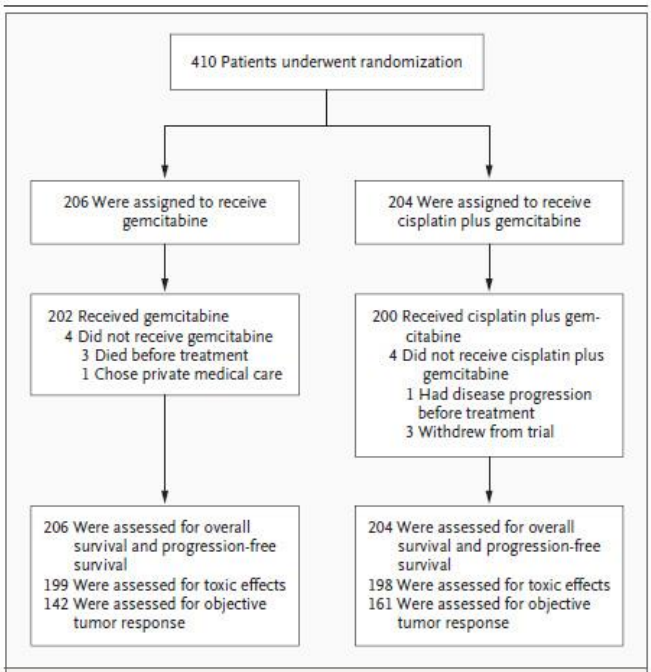

Figure 1. Patient Enrollment, Randomization, and Treatment.
Measurable disease was not a study-entry criterion; therefore, not all patients were assessed for an objective tumor response.

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Variable	Gemcitabine (N=206)	Cisplatin plus Gemcitabine (N=204)	P Value
Age — yr			
Median	63.2	63.9	0.88
Range	25.4–84.8	32.8–81.9	
Sex — no. (%)			
Female	108 (52.4)	108 (52.9)	0.92
Male	98 (47.6)	96 (47.1)	
Extent of disease — no. (%)			
Locally advanced	49 (23.8)	55 (27.0)	0.46
Metastatic	157 (76.2)	149 (73.0)	
Primary tumor site — no. (%)			
Gallbladder	76 (36.9)	73 (35.8)	0.87
Bile duct	119 (57.8)	122 (59.8)	
Ampulla	11 (5.3)	9 (4.4)	
Type of tumor — no. (%)			
Adenocarcinoma	191 (92.7)	186 (91.2)	0.27
Carcinoma, type not specified	12 (5.8)	17 (8.3)	
Adenosquamous carcinoma	2 (1.0)	0	
Squamous-cell carcinoma	1 (0.5)	0	
Carcinosarcoma	0	1 (0.5)	
ECOG performance-status score — no. (%)			
0	64 (31.1)	66 (32.4)	0.72
1	117 (56.8)	111 (54.4)	
2	24 (11.7)	27 (13.2)	
Unknown	1 (0.5)	0	
Previous therapy — no. (%)			
No	50 (24.3)	50 (24.5)	0.96
Yes	156 (75.7)	154 (75.5)	
Type of previous therapy — no. (%)			
Curative surgery	48 (23.3)	37 (18.1)	0.20
Palliative surgery	40 (19.4)	37 (18.1)	0.74
Laparotomy	49 (23.8)	48 (23.5)	0.95
Biliary stenting	92 (44.7)	93 (45.6)	0.85
Radiotherapy	5 (2.4)	3 (1.5)	0.48
Adjuvant chemotherapy	5 (2.4)	3 (1.5)	0.74
Photodynamic therapy	1 (0.5)	1 (0.5)	1.00
Other therapy	81 (39.3)	76 (37.3)	0.14

* ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning.

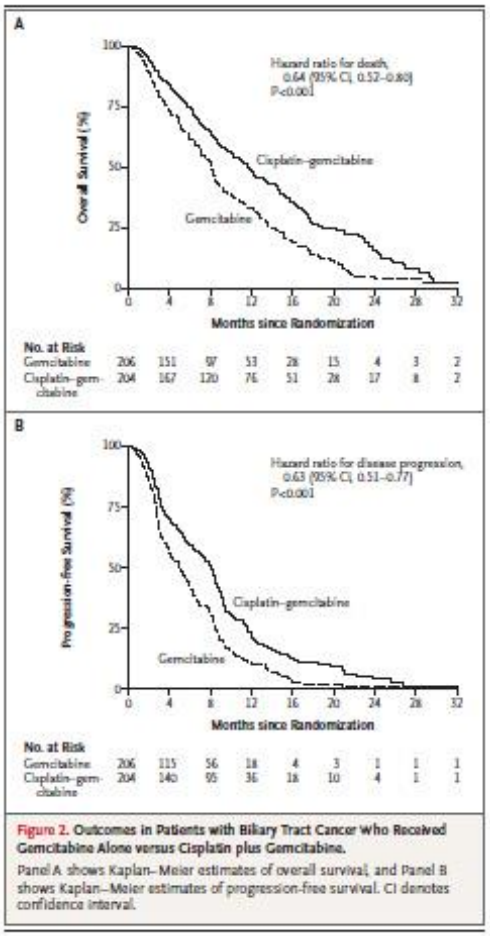

Figure 2. Outcomes in Patients with Biliary Tract Cancer Who Received Gemcitabine Alone versus Cisplatin plus Gemcitabine.

Panel A shows Kaplan–Meier estimates of overall survival, and Panel B shows Kaplan–Meier estimates of progression-free survival. CI denotes confidence interval.

Table 2. Grade 3 or 4 Toxic Effects during Treatment, According to Treatment Group.

Variable	Gemcitabine (N=199)	Cisplatin plus Gemcitabine (N=198)	P Value
	number (percent)		
Hematologic toxic effects			
Decreased white-cell count	19 (9.5)	31 (15.7)	0.07
Decreased platelet count	13 (6.5)	17 (8.6)	0.44
Decreased hemoglobin level	6 (3.0)	15 (7.6)	0.04
Decreased neutrophil count	33 (16.6)	50 (25.3)	0.03
Any hematologic toxic effect	47 (23.6)	64 (32.3)	0.05
Liver function			
Increased alanine aminotransferase level	34 (17.1)	19 (9.6)	0.03
Other abnormal liver function	39 (19.6)	26 (13.1)	0.08
Any abnormal liver function	54 (27.1)	33 (16.7)	0.01
Nonhematologic toxic effects			
Alopecia	0	2 (1.0)	0.16
Anorexia	5 (2.5)	6 (3.0)	0.75
Fatigue	33 (16.6)	37 (18.7)	0.58
Nausea	7 (3.5)	8 (4.0)	0.78
Vomiting	11 (5.5)	10 (5.1)	0.65
Impaired renal function	2 (1.0)	3 (1.5)	0.83
Infection			
Without neutropenia	23 (11.6)	12 (6.1)	0.05
With neutropenia	14 (7.0)	20 (10.1)	0.28
Biliary sepsis	8 (4.0)	8 (4.0)	0.99
Any type	38 (19.1)	36 (18.2)	0.82
Deep-vein thrombosis	1 (0.5)	4 (2.0)	0.18
Thromboembolic event	3 (1.5)	7 (3.5)	0.20
Other	62 (31.2)	66 (33.3)	0.64
Any	100 (50.3)	108 (54.5)	0.39
Any grade 3 or 4 toxic effect	137 (68.8)	140 (70.7)	0.69

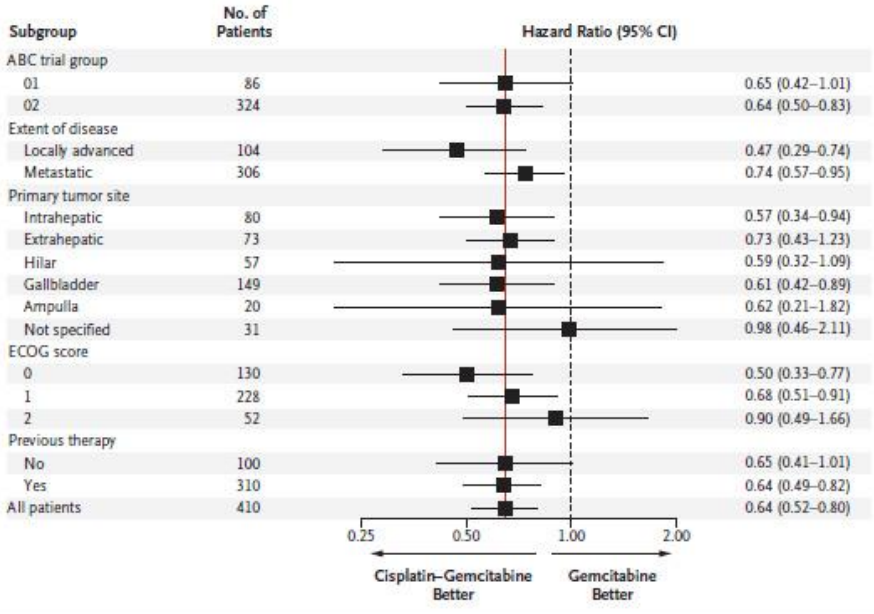

Figure 3. Hazard Ratio, According to Trial and Prespecified Baseline Factors.

ABC denotes Advanced Biliary Cancer, and ECOG Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning. The red line indicates the hazard ratio for death (0.64) in the intention-to-treat population.

3. 有効性

a. 奏効率

ゲムシタビン単独群：102/142(71.8%)，シスプラチン併用群：131/161(81.4%)，P=0.049

ゲムシタビン単独投与群に比較して，シスプラチン併用群の奏効率は有意に良好

b. 50%全生存期間（追跡期間中央値 8.2 ヵ月）

ゲムシタビン単独群：8.1 ヵ月，シスプラチン併用群：11.7 ヵ月

ハザード比 0.64，95%信頼区間 0.52−0.80，P<0.001

ゲムシタビン単独投与群に比較して，シスプラチン併用群の全生存期間は有意に良好

c. 50%無増悪生存期間

ゲムシタビン単独群：5.0 ヵ月，シスプラチン併用群：8.0 ヵ月

ハザード比 0.63，95%信頼区間 0.51−0.77，P<0.001

ゲムシタビン単独投与群に比較して，シスプラチン併用群の無増悪生存期間は有意に良好

4. サブグループ解析

進行程度，腫瘍部位，前治療にかかわらず，シスプラチン併用群の全生存期間が良好であることとが示されているが，PS=2 では有意差を認めていない。

5. 有害事象（グレード 3−4，両群に有意差を認めた項目のみ記載）

・ヘモグロビン減少　ゲムシタビン単独群：3.0%，シスプラチン併用群：7.6%，P=0.04
・好中球減少　ゲムシタビン単独群：16.6%，シスプラチン併用群：25.3%，P=0.03
・ALT 上昇　ゲムシタビン単独群：17.1%，シスプラチン併用群：9.6%，P=0.03

シスプラチン併用群は，好中球減少，ヘモグロビン減少などの血液毒性の頻度が高いが，ゲムシタビン単独群は，肝機能亢進，好中球減少なしの感染の頻度が高い。その他の有害事象は両群に有意差は認められない。

著者らの結論

シスプラチン単独群に比較して，シスプラチンとゲムシタビンの併用は，問題となる毒性が増加することなしに生存期間が有意に良好である。進行胆道がん患者の治療として，シスプラチンとゲムシタビンの併用は適切な選択肢である。