Second-line therapy for gemcitabine-pretreated advanced or metastatic pancreatic cancer

Romain Altwegg, Marc Ychou, Vanessa Guillaumon, Simon Thezenas, Pierre Senesse, Nicolas Flori, Thibault Mazard, Ludovic Caillo, Stéphanie Faure, Emmanuelle Samalin, Eric Assenat

Romain Altwegg, Marc Ychou, Vanessa Guillaumon, Simon Thezenas, Pierre Senesse, Nicolas Flori, Thibault Mazard, Ludovic Caillo, Stéphanie Faure, Emmanuelle Samalin, Eric Assenat, the Oncology and Digestive Endoscopy Department of the CRLC Val d’Aurelle, 34000 Montpellier, France

Author contributions: Altwegg R and Assenat E contributed equally to this work; Ychou M and Assenat E contributed to conception and design of this study; Altwegg R wrote this paper; Mazard T, Flori N and Caillo L performed acquisition of data; Thezenas S and Faure S performed analysis and interpretation of data; Guillaumon V, Senesse P, Samalin E and Assenat E critically revised this paper.

Correspondence to: Romain Altwegg, MD, the Oncology and Digestive Endoscopy Department of CRLC Val d’Aurelle, 34000 Montpellier, France. romain.altwegg@free.fr

Received: December 16, 2010 Revised: February 7, 2012
Accepted: February 27, 2012
Published online: March 28, 2012

Abstract

AIM: To investigate second-line chemotherapy in gemcitabine-pretreated patients with advanced or metastatic pancreatic cancer [(frequency, response, outcome, course of carbohydrate antigen 19-9 (CA 19-9)].

METHODS: This retrospective study included all patients with advanced or metastatic pancreatic cancer (adenocarcinoma or carcinoma) treated with second-line chemotherapy in our center between 2000 and 2008. All patients received first-line chemotherapy with gemcitabine, and prior surgery or radiotherapy was permitted. We analyzed each chemotherapy protocol for second-line treatment, the number of cycles and the type of combination used. The primary endpoint was overall survival. Secondary endpoints included progression-free survival, response rate, grade 3-4 toxicity, dosage modifications and CA 19-9 course.

RESULTS: A total of eighty patients (38%) underwent a second-line therapy among 206 patients who had initially received first-line treatment with a gemcitabine-based regimen. Median number of cycles was 4 (range: 1-12) and the median duration of treatment was 2.6 mo (range: 0.3-7.4). The overall disease control rate was 40.0%. The median overall survival and progression-free survival from the start of second-line therapy were 5.8 (95% CI: 4.1-6.6) and 3.4 mo (95% CI: 2.4-4.2), respectively. Toxicity was generally acceptable. Median overall survival of patients with a CA 19-9 level declining by more than 20% was 10.3 mo (95% CI: 4.5-11.6) vs 5.2 mo (95% CI: 4.0-6.4) for others (P = 0.008).

CONCLUSION: A large proportion of patients could benefit from second-line therapy, and CA 19-9 allows efficient treatment monitoring both in first and second-line chemotherapy.

© 2012 Baishideng. All rights reserved.

Key words: Second-line; Chemotherapy; Pancreatic cancer; Gemcitabine; Carbohydrate antigen 19-9

Peer reviewer: Dr. Gerardo Rosati, Medical Oncology Unit, S. Carlo Hospital, Via Potito Petrone, 1, Potenza 85100, Italy

Altwegg R, Ychou M, Guillaumon V, Thezenas S, Senesse P, Flori N, Mazard T, Caillo L, Faure S, Samalin E, Assenat E. Second-line therapy for gemcitabine-pretreated advanced or metastatic pancreatic cancer. World J Gastroenterol 2012; 18(12): 1357-1364

Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i12/1357.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i12.1357

INTRODUCTION

Pancreatic cancer is the tenth most common cause of cancer in the United States and the fourth leading cause...
of cancer death, with an estimated 42,000 new cases and 35,000 associated deaths in 2009[1]. In France, over 7,200 patients were diagnosed with a pancreatic cancer in 2008, and almost the same number died from their disease[2]. At the time of diagnosis, most of patients present with advanced or metastatic pancreatic cancer, thereby precluding surgical resection[3]. Gemcitabine has been considered as the standard treatment for advanced pancreatic cancer ever since a randomized trial demonstrated significant improvement in survival and clinical benefit over 5-FU[4]. However, its efficacy remains moderate with median overall survival (OS) times ranging from 5 to 8 mo, and one-year survival rates varying between 17% and 25%. Numerous studies have attempted to increase efficacy of chemotherapy by combining gemcitabine with other drugs, but most of the regimens evaluated in phase III trials failed to show any improvement in overall survival[5-18]. Only one randomized trial[4] (n = 569 patients) comparing gemcitabine alone vs gemcitabine combined with erlotinib showed a modest but significant increase in OS in the erlotinib arm (6.2 mo vs 5.9 mo, P = 0.025). Actually, the rate of patients receiving second-line chemotherapy varied from 16% to 57% in the trials evaluating a gemcitabine-based combination therapy[6-18]. This difference can be explained by both the deterioration in performance status after gemcitabine and the absence of recommended standard treatment in second-line[19]. Despite limited clinical data in this situation, a phase II trial comparing oxaliplatin/folinic acid/5-FU (OFF) combination vs best supportive care as second-line treatment in gemcitabine-pretreated patients with advanced pancreatic cancer showed substantial benefit in the chemotherapy arm, with an overall survival prolonged by 2.6 mo (P = 0.008)[20]. Serum carbohydrate antigen 19-9 (CA 19-9), the sialylated Lewis blood group antigen defined by the monoclonal antibody 1116 NS 19.9[21], is the most common tumor marker in Europe and in the United States for patients with pancreatic cancer, both as a prognostic factor and an early marker of response to treatment. To date, the reliability and prognostic value of CA 19-9 levels to monitor first-line chemotherapy of advanced pancreatic cancer patients is well established[8].

In this context, this study aimed to describe the frequency of gemcitabine-pretreated patients with advanced or metastatic pancreatic cancer receiving second-line chemotherapy, their overall survival and progression-free survival. We also investigated response rates, outcome and potential correlations between the level and course of CA 19-9 and survival.

MATERIALS AND METHODS

Patients
This retrospective study included all adult patients with an advanced or metastatic histologically proven pancreatic cancer (adenocarcinoma or carcinoma) initially treated with gemcitabine in our center between 2000 and 2008. All patients received first-line chemotherapy with gemcitabine at a dose of 1000 mg/m² once weekly for 7 wk followed by 1 wk of rest; thereafter, gemcitabine was given once weekly for 3 wk followed by 1 wk of rest until progression of disease. Prior surgery or radiotherapy for local disease was permitted. All patients’ medical records were registered within a computerized database [following national registry council (CNIL) authorization]. While there was no standard treatment used in second line, the treatment decision regarding a second-line therapy was systematically made by a multidisciplinary oncology committee according to the performance status, age and comorbidities.

Methods
We assessed each second-line chemotherapy protocol for the duration, the number of cycles and the type of drug combinations. The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), response rates, grade 3-4 toxicity, dosage modifications and CA 19-9 course. We stratified overall survival and progression-free survival according to the response to gemcitabine treatment (duration of treatment ≥ or < 4 mo) and the performance status (0-1 vs 2-3). Response rates and disease progression were evaluated after 2 mo of treatment by Response Evaluation Criteria in Solid Tumors[22] and clinical examination. Toxicity was assessed at each visit using the National Cancer Institute Common Toxicity Criteria v.2.0 (CTC AE v2.0). The CA 19-9 levels were determined from serum samples collected at baseline (maximum one month before starting treatment) and at final treatment evaluation. A value of 60 IU/mL was accepted as the upper limit of normal. A reduction in CA 19-9 level was considered as relevant when serum concentrations decreased by more than 20% after the completion of treatment.

Statistical analysis
In this retrospective study, information relating to identification, treatment, available biological material, surgery, response to therapy and outcome were collected for each patient. The primary objective was to evaluate the efficacy of a variety of second-line regimens in a large series of advanced pancreatic adenocarcinoma after first-line treatment with a gemcitabine-based regimen. Categorical variables were reported by contingency tables. Continuous variables were expressed as medians and ranges. The objective response rate was presented with a 95% CI. Survival rates and median values were estimated according to the Kaplan-Meier method. Patients alive at the tie of analysis were censored at their last follow-up examination. Overall survival duration was measured from the date of first infusion until death from any cause. Progression-free survival duration was calculated from the date of first infusion until the first disease progression. Survival curves were drawn, and the log rank test was performed to assess differences between groups. All reported P values are two-sided. For all statistical tests, differences were considered as significant at the 5% level. Statistical analyses were performed using the STATA 9.0 software.
RESULTS

Patient characteristics

Baseline characteristics of the study population are detailed in Table 1. Of 206 patients receiving a first-line gemcitabine-based treatment for advanced or metastatic pancreatic cancer, 80 patients (38%) underwent a second-line therapy between January 2000 and May 2008. The median age was 61 years (range 36-81 years), and 38 patients were male (47.5%). The diagnosis of cancer was histologically confirmed in 67 patients (83.8%). Thirty-seven patients had undergone surgery including a pancreatoduodenectomy (n = 25) and palliative operation (n = 12) before first-line chemotherapy. Three other patients had received external radiation therapy. An endoscopic biliary prosthesis had been inserted prior to chemotherapy in eight patients. All patients received first-line chemotherapy with gemcitabine, with a median of 3 cycles (range: 1-12) and a median duration of 3.3 mo. Twenty-nine patients (36.2%) were treated for more than 3 cycles (range: 1-12) and a median duration of 3.3 mo. A total of 77 patients (96.3%) had evidence of metastatic disease, for most of them localized in the liver (70.1%). Despite the advanced stage of disease, patients generally showed good performance status before initiating second-line treatment, the WHO PS was of 0-1 in 71 patients (88.7%) and ≥ 2 in nine patients (11.3%).

From the CA 19-9 analyses performed in 64 patients, fifty-seven (89.1%) showed an elevated level, and initial median serum concentration was 741.5 IU/mL (range: 2-2000 IU/mL).

Treatment

The median number of second-line chemotherapy cycles was 4 (range: 1-12) and the median duration of treatment was 2.6 mo (range: 0.3-7.4).

All treatment regimens are described in Table 2. Different drug combinations were used in second-line. Twenty-three patients (28.8%) received a treatment with cisplatin (cisplatin group), 22 patients (27.5%) with irinotecan (irinotecan group) and 21 patients (26.3%) with oxaliplatin (oxaliplatin group). Fourteen patients (17.5%) were given other treatment, including a single agent for four of them. The duration of treatment did not significantly differ between groups (Table 3).
Response and survival

There was no complete response. Six patients (7.5%) achieved a partial response, 26 patients (32.5%) a disease stabilisation, 44 patients (55.0%) experienced disease progression and 4 patients could not be assessed. The overall disease control rate (complete response, plus partial response, plus stable disease) was 40.0% (median follow-up was 6.0 mo).

The median OS from the start of second-line therapy was 5.8 mo (95% CI: 4.1-6.6 mo). The 1-year and 2-year OS rates were 13.6% (95% CI: 6.9-22.7 mo) and 6.1% (95% CI: 2.0-13.5 mo), respectively (Figure 1A). The median PFS from the start of second-line therapy was 3.4 mo (95% CI: 2.4-4.2 mo). The one-year and two-year PFS rates were 6.0% (95% CI: 1.8-13.9 mo) and 4.0% (95% CI: 0.8-11.5 mo), respectively (Figure 1B). There was no significant difference between the four chemotherapy groups for overall disease control rates, overall survival and progression-free survival ($P > 0.05$) (Table 3).

The median OS was 6.3 mo (95% CI: 4.3-7.2 mo) in patients with a performance status of 0-1 (71 patients) vs 1.8 mo (95% CI: 0.3-5.9 mo) in patients with a PS > 1 (9 patients) ($P < 0.001$). The one-year OS rates were 16.0% and 0%, respectively. The median PFS was 3.4 mo (95% CI: 2.6-4.9 mo) in patients with a performance status of 0-1 vs 2.1 mo (95% CI: 0.5-3.0 mo) in patients with a PS > 1 ($P = 0.004$). The one-year PFS rates were 7.0% and 0%, respectively.

The median OS times were 7.2 mo (95% CI: 4.5-10.5 mo) in patients treated for more than 4 mo with gemcitabine as first-line therapy (29 patients) and 4.2 mo (95% CI: 3.2-5.9 mo) in those treated less than 4 mo (51 patients) ($P = 0.046$). The one-year PFS rates were 10.0% and 4.0%, respectively.

Toxicity and dosage modifications

Toxicity was generally acceptable. The incidence of severe adverse events (grade 3-4) is reported on Table 4. Twenty-seven patients (33.7%) experienced at least one grade 3-4 toxic event. Neutropenia was the most frequent haematological toxicity, occurring in 14 patients (17.1%). There were 5 chemotherapy-related deaths. Two deaths were attributed to sepsis, and three to a combination of cancer and treatment-related complications. There was no difference in the incidence of toxicity and treatment-related deaths between the four chemotherapy groups (Table 5).

Forty-one patients (51.3%) had dosage modifications, including treatment suppression for 7 patients, dose reduction for 17 patients and cycle delay for 33 patients. Dose reductions were caused by haematological (9 patients, 53%) or clinical toxicities (8 patients, 47%) (Table 6). In thirty-one patients (41.3%), the chemotherapy was discontinued before evaluation because of disease progression (74.2%), toxicity (9.7%) or death (16.1%). There was no significant difference between groups for dose modification and chemotherapy discontinuation before evaluation.

Carbohydrate antigen 19-9 measurement and survival

Reduction in CA 19-9 levels during treatment was associated with improved survival. The median OS was significantly higher in patients whose level of CA 19-9 declined by more than 20% when compared to other patients 10.3 mo (95% CI: 4.5-11.6) vs 5.2 mo (95% CI: 4.0-6.4) ($P = 0.008$) (Figure 2A). In this subgroup of patients, the median PFS was 6.7 mo (95% CI: 3.3-8.8 mo) vs 3.4 mo (95% CI: 2.6-4.2 mo) ($P = 0.031$) (Figure 2B). All patients who experienced a CA 19-9 reduction > 20% achieved disease control (3 partial responses and 5 cases of stable disease).

DISCUSSION

If gemcitabine-based chemotherapy is the current standard of care for first-line treatment of advanced pancreatic cancer, there are limited data to support a standard second-line chemotherapy regimen. Indeed, the true survival benefit from first-line therapy is small, and few patients can endure a second line as their performance status deteriorates with disease progression. In our study, the rate of patients treated with second-line chemotherapy was 38.8%, in accordance with most published data regarding gemcitabine-pretreated pancreatic cancer (16%-57%). Median overall survival from the start of second-line setting was 5.6 mo (4.1-6.6 mo), and median progression-free survival was 3.4 mo (2.4-4.2 mo). These results are similar to those obtained in first-line with gemcitabine by Burris et al. or Heinemann et al.
patients with good performance status can benefit from second-line chemotherapy after first-line gemcitabine-based treatment, with appreciable overall and progression-free survivals. This retrospective study included a large population, while most of data published over the last ten years involved relatively small samples in monotherapy (from 13 to 52 patients) as well as in bitherapy (from 12 to 46 patients). The disease control rate was 40%, as described by many authors for both monotherapy and bitherapy regimens, and median overall and progression-free survivals were superior to those reported in monotherapy studies, but were not different from bitherapy.

In daily practice, second-line therapies are regularly used in gemcitabine-pretreated patients with pancreatic carcinomas, but the efficacy and benefit in terms of survival or quality of life have never been validated. A randomized phase III trial conducted in second line was presented by Pelzer et al. One hundred and sixty-five gemcitabine-pretreated patients with pancreatic cancer were randomly assigned to receive either FF (5-FU 2 g/m² on days 1, 8, 15 and 22) or OFF (FF plus oxaliplatin 85 mg/m² on days 1, 8, 15 and 22). Median overall survival and progression-free survival were significantly improved with OFF protocol (20 wk vs 13 wk, P = 0.014; and 13 wk vs 9 wk, P = 0.012, respectively), with an acceptable tolerance profile. This study illustrated the effectiveness of this protocol which may become the standard second-line treatment, with appreciable overall and progression-free survivals.

Moreover, patients with good performance status (0-1) and who had benefited from gemcitabine chemotherapy in first line (duration of treatment ≥ 4 mo) had a significantly greater duration of overall survival than those who had not (6.3 mo vs 1.8 mo, P < 0.001; and 7.2 mo vs 4.2 mo, P = 0.046, respectively). The rate of grade 3-4 toxicity was determined to be 33.7% (27 patients), but there were no unexpected side effects. Consequently, our experience demonstrates that a selected population of patients with satisfactory performance status in

### Table 4 Toxicity, dosage modifications and chemotherapy discontinuation n (%)

| Type                        | Patients |
|-----------------------------|----------|
| Clinical toxicity grade 3-4 |          |
| Nausea                      | 3 (3.7)  |
| Vomiting                    | 5 (6.2)  |
| Diarrhea                    | 2 (2.4)  |
| Stomatitis                  | 1 (1.2)  |
| Fever                       | 6 (7.5)  |
| Infection                   | 6 (7.5)  |
| Haematological toxicity grade 3-4 |          |
| Anemia                      | 2 (2.4)  |
| Neutropenia                 | 14 (17.1)|
| Thrombocytopenia            | 1 (1.2)  |
| Dosage modifications        | 41 (51.3)|
| Type                        |          |
| Treatment suppression       | 7 (17.1) |
| Dose reduction              | 17 (41.5)|
| Delay of cycle              | 33 (80.5)|
| Discontinuation before evaluation | 31 (41.3)|
| Progressive disease         | 23 (74.2)|
| Toxicity                    | 3 (9.7)  |
| Chemotherapy-related deaths | 5 (16.1) |

### Table 5 Toxicity for chemotherapy groups n (%)

| Group                         | Patients |
|-------------------------------|----------|
| Cisplatin                     |          |
| Informed Pancrocan group      |          |
| Oxaliplatin                   |          |
| Other group                   |          |
| Clinical toxicity grade 3-4   |          |
| Nausea                        | 3 (14.3) |
| Vomiting                      | 5 (5.3)  |
| Diarrhea                      | 1 (4.8)  |
| Stomatitis                    | 0 (0)    |
| Fever                         | 0 (0)    |
| Haematological toxicity grade 3-4 |          |
| Anemia                        | 1 (1.2)  |
| Neutropenia                   | 14 (17.1)|
| Thrombocytopenia              | 0 (0)    |

NS: Not significant.

### Table 6 Dose reduction n (%)

| Dose reduction                | Patients |
|-------------------------------|----------|
| Neutropenia grade 2 or 3-4    | 5 (6.2)  |
| Thrombocytopenia grade 2      | 4 (5.0)  |
| Hand-foot skin reaction grade 2| 5 (6.2)  |
| Neutropenia grade 2           | 2 (2.4)  |
| Diarrhea grade 3-4            | 1 (1.2)  |

Figure 2 Overall survival and carbohydrate antigen 19-9 evolution in second line. A: Overall survival; B: Progression-free survival. Ev. Ca 19-9: Course of carbohydrate antigen 19-9.
clinical trials, and recommend the use of oxaliplatin and fluoropyrimidine if enrolment in trials is not possible[20,27]. Finally, the XELOX regimen[28] showed comparable efficacy to FOLFOX (or OFF) regimen, while offering the advantage of oral fluoropyrimidine treatment. Even so, more large randomized controlled trials are required in second line before a new standard of care can be established.

Interestingly, the CA 19-9 measurement was correlated with OS and PFS in our study. Patients whose level of CA 19-9 declined by more than 20% had a significantly greater duration of survival. The prognostic value of CA 19-9 level and course is well established for patients with pancreatic cancer treated with surgery[23-31], radiotherapy and chemoradiotherapy[22,28]. Some studies also correlated the level and the course of CA 19-9 with OS and PFS of pancreatic cancer patients treated with gemcitabine as first-line chemotherapy[32-34]. These studies showed improved median OS for patients with a decrease of CA 19-9 > 20% after two months of treatment with gemcitabine. Saad et al[37] reported an increase in the median OS for patients with a reduction of CA 19-9 at any time after treatment. In second-line, only one study demonstrated that a CA 19-9 value > 400 IU/mL was a significant independently negative prognostic factor[38]. To our knowledge, it was the second report which showed a correlation between OS and CA 19-9 course[39], and the first report for PFS and CA 19-9 course in second-line chemotherapy for gemcitabine-pretreated patients with pancreatic cancer.

In summary, treatment of metastatic pancreatic cancer remains a major challenge and requires new chemotherapeutic and targeted agent combination to be compared to gemcitabine in first-line. It should be noted that a new therapeutic alternative could merge in first-line for selected patients according to the recent results obtained in a randomized Phase III study comparing FOLFIRINOX regimen to gemcitabine[36]. A significant longer overall survival, progression-free survival, and higher response rates were obtained with FOLFIRINOX than with gemcitabine alone, associated with manageable toxicities.

The present study focused on second-line therapy in gemcitabine-pretreated patients with advanced pancreatic cancer. From our experience, second-line chemotherapy is a valuable treatment option after progression on gemcitabine-based regimen, because 30% to 40% of patients could benefit from this therapy, especially those with good performance status (1-2) and who gained benefit from first-line therapy. Further randomized clinical trials are necessary to provide a standard treatment in this situation. Additionally, measurement of the CA 19-9 level was confirmed to be an efficient marker for treatment monitoring in first-line as well as in second-line treatment.

REFERENCES
1 National Cancer Institute, Surveillance Epidemiology and End Results. Pancreas. SEER Stat Fact Sheets. Availble from: URL: http://seer.cancer.gov/statfacts/html/pancreas.html
2 Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010; 46: 765-781
3 Ziske C, Schlie C, Gorschützer M, Glaßmacher A, Møy U, Strehl J, Sauerbruch T, Schmidt-Wolf IG. Prognostic value of CA 19-9 levels in patients with inoperable adenocarcinoma of the pancreas treated with gemcitabine. Br J Cancer 2003; 89: 1413-1417
4 Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial. J Clin Oncol 1997; 15: 2403-2413
5 Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Cregg A, Adab F, Thompson J, Leonard P, Ostrowski J, Eato C, Scheithauer W, Herrmann R, Neoptolemos JP. Phase III randomized comparison of gemcitabine versus gemcitabine plus capcitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009; 27: 3513-3518
6 Moore MJ, Coldstein D, Hamm J, Figer A, Hecht JR, Gallerger S, Au HJ, Murawwa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Pasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007; 25: 1960-1966
7 Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 2002; 20: 3270-3275
8 Herrmann R, Bodoky G, Ruhlstaetter T, Gilmeilus B, Bajetra E, Schüller J, Saleli P, Bauer J, Figer A, Pestalozzi B, Köhne CH, Mingrone W, Stemmer SM, Kornk GV, Koehberger D, Cina S, Bernhard J, Dietrich D, Scheithauer W. Gemcitabine
versus best supportive care alone (BSC) in second-line therapy of gemcitabine-refractory advanced pancreatic cancer (CONKO 003). J Clin Oncol 2005; 23: 4031

21 Kropowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. Somatic Cell Genet 1979; 5: 957-971

22 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oostrom AT, Christian MC, Coyley SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205-216

23 SNFGE. Thésaurus de cancérologie digestive. Available from: URL: http://www.thesaurus-cancerologie.org/

24 Kang SP, Saif MW. Optimal second line treatment options for gemcitabine refractory advanced pancreatic cancer patients. Can we establish standard of care with available data? JOP 2008; 9: 83-90

25 Pelzer U, Kubica K, Stieeler J, Schwanner I, Heil G, Görner M, Mölle M, Hilgab A, Dörken B, Riess H, Oettle H. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 2008; 26: A4058

26 NCCN. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma V.1.2009. Available from: URL: http://www.nccn.org/Professionals/Provider_Resources/Guidelines/Pancreas/PancreatAdenocarcinoma/v1/2009.pdf

27 Gounaris I, Zaki K, Corrie P. Options for the treatment of gemcitabine-resistant advanced pancreatic cancer. JOP 2010; 11: 113-123

28 Xiong HQ, Varadhachary GR, Blais JC, Hess KR, Abbuzzese JL, Wolff RA. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 2008; 113: 2046-2052

29 Glenn J, Steinberg WM, Kurtzman SH, Steinberg SM, Sin德尔 WR. Evaluation of the utility of a radioimmunoassay for serum CA 19-9 levels in patients before and after treatment of carcinoma of the pancreas. J Clin Oncol 1988; 6: 462-468

30 Hernandez JM, Cowgill SM, Al-Saadis S, Collins A, Ross SB, Cooper J, Villalodid D, Zervos E, Rosemurgy A. CA 19-9 velocity predicts disease-free survival and overall survival after pancreactectomy of curative intent. J Gastrointest Surg 2009; 13: 349-353

31 Berger AC, Garcia M, Hoffman JP, Regine WF, Abrams RA, Safran H, Konski A, Benson AB, MacDonald J, Willett CG. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. J Clin Oncol 2008; 26: 5918-5922

32 Katt A, Haunton A, Lanciano R, Hoffman J, Coia L. Prognostic value of CA 19-9 levels in patients with carcinoma of the pancreas treated with radiotherapy. Int J Radiat Oncol Biol Phys 1998; 41: 393-396

33 Koom WS, Seong J, Kim YB, Pyun HO, Song SY. CA 19-9 as a predictor for response and survival in advanced pancreatic cancer patients treated with chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009; 73: 1148-1154

34 Halm U, Schumann T, Schiefke I, Witzigmann H, Mösner J, Keim V. Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. Br J Cancer 2000; 82: 1013-1016

35 Maisey NR, Norman AR, Hill A, Massey A, Oates J, Cunningham D. CA19-9 as a prognostic factor in inoperable pancreatic cancer: the implication for clinical trials. Br J Cancer 2003; 89: 740-741

36 Nakai Y, Kawaite T, Isayama H, Sasaki T, Yagioka H, Yamahara Y, Kogure H, Arizumi T, Togawa O, Ito Y, Matsubara S, Kihara K, Sasahira N, Tsujino T, Tada M, Oyama M. CA 19-9 response as an early indicator of the effectiveness of gem-
citabine in patients with advanced pancreatic cancer. Oncology 2008; 75: 120-126

37 Saad ED, Machado MC, Wajsbrot D, Abramoff R, Hoff PM, Tabacof J, Katz A, Simon SD, Gansl RC. Pretreatment CA 19-9 level as a prognostic factor in patients with advanced pancreatic cancer treated with gemcitabine. Int J Gastrointest Cancer 2002; 32: 35-41

38 Marechal R, Demois A, Gay F, De Maertelaere V, Arvanitaki M, Hendliss A, Van Laethema JL. Prognostic factors and prognostic index for chemonaive and gemcitabine-refractory patients with advanced pancreatic cancer. Oncology 2007; 73: 41-51

39 Haas M, Laubender RP, Stieber P, Holdenrieder S, Bruns CJ, Wilkowski R, Mansmann U, Heinemann V, Boeck S. Prognostic relevance of CA 19-9, CEA, CRP, and LDH kinetics in patients treated with palliative second-line therapy for advanced pancreatic cancer. Tumour Biol 2010; 31: 351-357

40 Conroy T, Desseigne F, Ychou M, Ducreux M, Bouche O, Guimbaud R, Fncikc-flld Prodigit Group. Randomized phase III trial comparing Folfinox (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE. J Clin Oncol 2010; 28: 4010

S- Editor Cheng JX  L- Editor A  E- Editor Xiong L