Artigo Original

FURTHER EVIDENCE OF THE PROGNOSTIC ROLE OF PRETREATMENT LEVELS OF CA 19-9 IN ADVANCED PANCREATIC CANCER

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SUMMARY

Objective. We and others have previously suggested that pretreatment levels of CA 19-9 correlate with overall survival (OS) among patients with advanced pancreatic cancer treated with gemcitabine. We sought to confirm the prognostic role of the pretreatment level of CA 19-9 in patients with advanced pancreatic cancer treated with chemotherapy.

Methods. We retrospectively identified 50 patients with locally advanced or metastatic pancreatic cancer treated in the first-line with single-agent gemcitabine or combinations. Patients could also have received second-line treatment. Kaplan-Meier estimates of OS were compared with the log-rank test, and multivariate analysis was done using the Cox model.

Results. Twenty-seven patients were female with a mean age of 64.3 years, and 82% were metastatic upon diagnosis. The median OS for the entire sample was 11 months, and the median CA 19-9 level was 542 U/mL. Significant predictors of OS in univariate analyses were the first-line use of combined chemotherapy (p=0.006) and use of erlotinib in any line (p=0.002), with borderline significance for pretreatment levels of CA 19-9 (p=0.052). In multivariate analysis, only use of erlotinib (p=0.003) and pretreatment CA 19-9 level (p=0.026) were significantly associated with OS.

Conclusion. Our study lends further support to use of the pre-chemotherapy level of CA 19-9 as a prognostic indicator in clinical practice and as a stratification factor in clinical trials. The association between erlotinib use and OS may have been biased by patient selection, notwithstanding the positive results from a previous randomized trial.

Key words: Pancreatic neoplasms. Drug therapy. Multivariate analysis. Survival analysis.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States and in the European Union.[1, 2] Among developing countries, the highest rates of pancreatic cancer are in Central and South America.[3, 4] Furthermore, pancreatic cancer is an important cause of cancer-related morbidity, and 5-year survival rates for the disease are still dismal.[5] Although surgical resection of early-stage disease remains the only potentially curative treatment modality, most patients present with or develop metastatic disease. For these patients, gemcitabine-based chemotherapy is the chief therapeutic modality, notwithstanding the low objective response rates.[6]

In pancreatic cancer, objective responses to chemotherapy are not only infrequent, but also difficult to evaluate using radiographic methods.[7] The endpoints collectively referred to as clinical benefit (pain, performance status, and weight loss) have been used in some studies reported in the past decade.[6, 8] In addition, the serum carbohydrate antigen CA 19-9 (the sialylated Lewis[a] blood group antigen) is a useful marker in pancreatic cancer. CA 19-9 is elevated in approximately 90% of patients with pancreatic adenocarcinoma,[9] and the levels of this marker have been shown to be of prognostic significance among patients undergoing treatment with surgery,[10, 11] radiation therapy,[12] and chemotherapy.[13] Decreasing levels of CA 19-9 after chemotherapy predict a longer survival among patients treated with single-agent,or combinations containing gemcitabine.[13-17] Following the initial observation by Halm *et al.*,[16] our group suggested a strong prognostic role for pretreatment levels of CA 19-9 among patients undergoing

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chemotherapy with gemcitabine,[17] a finding later corroborated by other investigators.[18-20] In the present study, we sought to confirm the prognostic role of pretreatment levels of CA 19-9 in an independent sample of patients. In addition, we investigated other potential prognostic markers among patients with pancreatic cancer undergoing systemic therapy.

Methods

We reviewed the charts of all patients with pancreatic cancer who had been treated at a single institution (Centro Paulista de Oncologia) between June 1999 and May 2005. No consent for this study was obtained from patients, given its retrospective nature and that most patients were deceased when this analysis was planned and carried out. Furthermore, treatment was always administered as part of routine medical care and no experimental agents were used. Eligible patients for the current analysis were those treated with at least one cycle of single-agent gemcitabine or a combination containing this agent for locally advanced or metastatic pancreatic adenocarcinoma. None of the patients in the study had been previously included in our original sample.[17] Of the 57 eligible patients screened for inclusion in the analysis, 50 were actually included, whereas the other seven patients were lost to follow-up.

Patients treated with single-agent gemcitabine had typically received initial weekly doses of 1000 mg/m^2, with adjustments dictated by clinical tolerance. Each cycle of therapy consisted of 3 consecutive treatment weeks, followed by a 1-week rest. Gemcitabine combinations in the first-line had been administered with oxaliplatin to the vast majority of patients using combinations, although some patients had been treated with gemcitabine combined with cisplatin[21] or with irinotecan.[22] Since some patients, who had been treated with single-agent gemcitabine had also received a second drug combined with gemcitabine (after tolerance to gemcitabine had been ascertained) before disease progression, all such regimens were considered as first-line treatment during this analysis. The same was done in the case of patients who had initially been treated with a combination, and in whom gemcitabine had been maintained as a single-agent (in order to decrease toxicity) until the first documentation of disease progression. During treatment, chemotherapy doses were reduced according to usual guidelines, and treatment was continued until clinical or radiographic evidence of disease progression or unacceptable toxicity. In addition to chemotherapy, some patients had been treated after first-line with a molecularly targeted agent such as erlotinib, bevacizumab and/or cetuximab. Since the oral tyrosine-kinase inhibitor erlotinib had been used more frequently, according to results of a phase III clinical trial,[23] only this molecularly targeted agent was analyzed in the study. Serum levels of CA 19-9 had been obtained before treatment initiation using commercially available assays.

Baseline demographic and clinical characteristics were retrieved from the patient charts and tabulated for analysis. Survival, measured from the beginning of systemic treatment until death, was estimated by the Kaplan-Meier method. Survival curves were compared using the log-rank test. The influence on survival of potential prognostic factors was assessed by multivariate analysis with the Cox proportional hazards model, using backward selection of variables. The total number of variables included in the model would limit to 10 the number of events per variable.[24] All statistical tests were two-sided, and p values <0.05 were considered statistically significant. Statistical analysis was performed using the MedCalc (version 9.3.1) statistical package.

Results

Patient characteristics

Selected demographic and clinical characteristics of the 50 patients are shown in Table 1. Ages ranged from 44 to 88 years (mean, 64.3), and 27 patients (54%) were female. Forty-one patients (82%) had metastatic disease upon diagnosis, whereas nine (18%) had locally advanced disease. Treatment regimens used in the first-line were gemcitabine (N=29), single-agent gemcitabine followed by gemcitabine combination (N=9), gemcitabine combination (N=7), and gemcitabine combination followed by single-agent gemcitabine (N=5). The latter three were combined for the analyses presented henceforward. Second- and third-line treatment was administered to 48% and 14% of patients, respectively and approximately one-third of patients had been treated with erlotinib. The median pretreatment serum level of CA 19-9 was 542 units/mL (range <2 to $>100,000$ units/mL).

Univariate analyses of overall survival

Forty-six of the 50 (92%) patients had died at the time of this analysis, and the estimated median overall survival (OS) was 11.0 months for the entire sample. The prognostic impact on overall survival of selected variables was investigated by Kaplan-Meier curves. Such variables included age, gender, stage, pretreatment CA 19-9 levels, type of treatment in the first-line, use of second-line chemotherapy, and use of erlotinib. The unadjusted p values for these variables are shown in Table 2. Pretreatment levels of CA 19-9 above the median were associated with a marginally significant improvement in survival (Figure 1, panel A). Only the use of combinations (Figure 1, panel B) and use of erlotinib (Figure 1, panel C) were significant predictors of overall survival in these univariate analyses.

Multivariate analysis of overall survival

The next step in the study was a multivariate analysis of the potential prognostic factors for OS. This analysis included the three variables with the highest association with OS in univariate analyses (use of combinations, use of erlotinib, and pretreatment CA 19-9). As shown in Table 2, the only statistically significant association with OS was for use of erlotinib and pretreatment level of CA 19-9. Patients with a CA 19-9 value equal to or below the median of 542 units/mL had an adjusted hazard ratio for mortality of 0.49 (95% confidence interval [CI], 0.27 - 0.91, p=0.026), when compared to patients with a CA 19-9 level above the median. In addition, use of erlotinib was significantly associated with an improved OS (hazard ratio, 0.33, 95% CI 0.16 - 0.68, p=0.003).

Table 1. Patient and treatment characteristics

Characteristic	Number (%)
Age, years	
Range (mean)	44 - 88 (64.3)
Gender	
Female	27 (54)
Male	23 (46)
Stage upon diagnosis	
Metastatic	41 (82)
Locally advanced	9 (18)
Pretreatment CA 19-9 level, units/mL	
Median (range)	524 (<2 to > 100,000)
Type of first-line therapy	
Single-agent gemcitabine	29 (58)
Single-agent gemcitabine followed by gemcitabine combination	9 (18)
Gemcitabine combination	7 (14)
Gemcitabine combination followed by single-agent gemcitabine	5 (10)
Use of subsequent lines of therapy after first line	
No	26 (52)
Second line only	17 (34)
Second and third lines	7 (14)
Use of erlotinib	
No	34 (68)
Yes	16 (32)

Table 2. Results of univariate and multivariate analyses

Variable	Univariate analysis	Multivariate analysis	
	p value	Hazard ratio* (95% CI)	p value
Age	0.958	NA	NA
Gender	0.140	NA	NA
Stage	0.126	NA	NA
Pretreatment CA 19-9 below the median	0.052	0.49 (0.27 - 0.91)	0.026
Use of first-line combination	0.006	NA	NA
Use of second-line chemotherapy	0.226	NA	NA
Use of erlotinib	0.002	0.33 (0.16 - 0.68)	0.003

* Adjusted hazard ratio for comparison with reference category for each variable.
CI, Confidence interval; NA, not applicable.

Figure 1 — Panel A

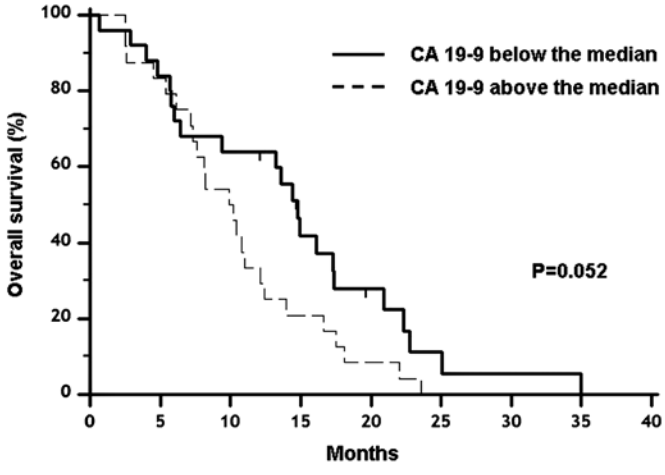


Figure 1 — Panel B

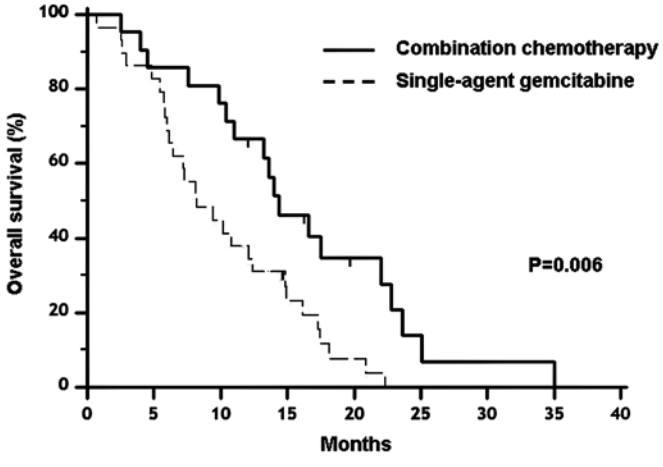
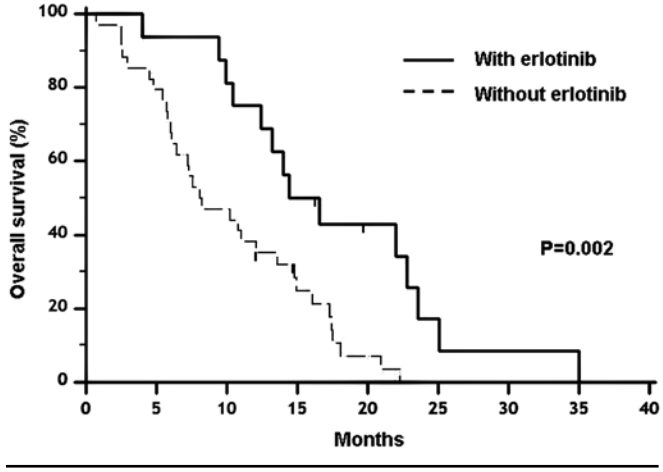


Figure 1 — panel C



Discussion

The present study confirms our previous finding that pretreatment CA 19-9 levels are of prognostic significance in patients with advanced pancreatic cancer treated with chemotherapy.[17] The cutoff point for CA 19-9 level is still not clear, since the median value in our previous study was 1,212 units/mL, compared with 542 units/mL in the current sample of patients. Further, other authors have found median levels ranging from 958 to 1,515 units/mL.[16, 19] Since CA 19-9 is a continuous variable, determination of a cutoff level, although appealing and necessary for the clinician, is more difficult to justify on biological grounds.

Previous studies have shown that pretreatment levels of CA 19-9 correlate with tumor burden or resectability among patients with clinically localized pancreatic cancer.[10, 25-27] The retrospective findings from our group and prospective findings from other investigators,[18, 19] show that pretreatment levels of CA 19-9 correlate with overall survival in advanced disease. Thus, it is conceivable that higher pretreatment levels of this marker correlate with an increased tumor burden, and therefore a worsened outlook, also in advanced disease. In line with this hypothesis, Rocha Lima *et al.* have found a statistically significant correlation between changes in CA 19-9 levels and changes in tumor measurements during treatment with gemcitabine and irinotecan.[22] On the other hand, it is also possible that an increased serum level of CA 19-9 is a marker for disease aggressiveness, thus representing a qualitative, rather than quantitative, indicator of tumor biology, a hypothesis that, to our knowledge, remains to be tested.

Other potential baseline prognostic factors such as tumor stage and patient gender have not proven significant predictors of overall survival in this or in our previous study, which included 28 patients.[17] Although both of these factors have had prognostic significance in multivariate analyses of prospective trials,[18, 21, 23] only one of these studies included pretreatment CA 19-9 in such analysis.[18] In this study Louvet *et al.*,reported CA 19-9 to be an independent prognostic factor in patients treated with gemcitabine or gemcitabine plus oxaliplatin. One limitation of our study was the fact that performance status, an important prognostic factor in pancreatic cancer,[18, 21] could not be evaluated in the current sample.This information, although easy to obtain, had not been recorded prospectively using currently available scores in most of our patients.

One important treatment-related variable, the use of combination regimens, although significant in univariate analysis, was not significant in multivariate analysis. This finding suggests that patient and tumor characteristics, rather than treatment itself, are the ultimate determinants of prognosis in advanced pancreatic cancer, notwithstanding the retrospective nature of our study and results from recent trials showing a slight survival benefit with use of selected combinations in the first-line.[28] Of note, however, several individual phase III trials of combination chemotherapy in advanced pancreatic cancer have had negative results.[21, 29, 30]

The use of erlotinib, whose combination with gemcitabine slightly improves survival in comparison with single-agent gemcitabine,[23] was found to be the strongest among the prognostic factors analyzed in our study. We cannot explain this finding, but it is conceivable that the non-randomized decision to use erlotinib has introduced confounding factors for this analysis. In addition, it should be kept in mind that the previous enthusiasm with targeted therapy[31] has been tempered by negative results from recent phase III trials investigating bevacizumab and cetuximab.[5] Even the small, 2-week survival advantage conferred by use of erlotinib has been questioned on the grounds of increased risk of toxicity.[32] Moreover, we interpret the finding of a prognostic impact for erlotinib use, as exploratory in nature, since our primary aim was to investigate the prognostic role of pretreatment CA 19-9 level.

Given the apparent role of pretreatment CA 19-9 level as an independent prognostic factor and as a potential surrogate marker for tumor burden or aggressiveness in advanced pancreatic cancer, imbalances in baseline CA 19-9 levels between groups of patients may account for some of the differences observed in comparative studies and also between different studies.[33] In that case, patient stratification for randomized trials should include pretreatment levels of CA 19-9 as a factor, a hypothesis worthy of further investigation in future studies.

Conclusion

The current study confirms that pretreatment CA 19-9 level is correlated with overall survival of patients with advanced pancreatic cancer receiving gemcitabine-based therapy. The optimal cut-off for prognostic stratification using this continuous variable remains unclear. However, we suggest that investigators responsible for previous, ongoing, and future studies attempt to further examine the prognostic role of CA 19-9, as well as the use of this tumor marker as a stratification factor in randomized trials.

Conflict of interest: none

Resumo

Evidência adicional do papel prognóstico do nível pré-tratamento de CA 19-9 em câncer de pâncreas avançado

Objetivo. Estudos anteriores pelo nosso grupo e por outros autores sugerem que o nível pré-tratamento do marcador tumoral CA 19-9 se correlaciona com a sobrevida global (SG) em pacientes com câncer de pâncreas avançado tratados com gencitabina. Nosso objetivo foi o de confirmar o papel prognóstico do nível pré-tratamento do CA 19-9 em pacientes com câncer de pâncreas avançado tratados com regimes variados de quimioterapia.

Métodos.Identificamos retrospectivamente 50 pacientes com câncer de pâncreas localmente avançado ou metastático tratados em primeira linha com gencitabina ou combinações contendo esse agente. Os pacientes poderiam ter recebido ainda tratamento em segunda linha com outros agentes. As estimativas de SG pelo método de Kaplan-Meier foram comparadas pelo teste log-rank, e a análise multivariada foi feita usando-se o modelo de Cox. Resultados. Vinte e sete pacientes eram do sexo feminino, a idade média foi de 64,3 anos, e 82% tinham doença metastática ao diagnóstico. A mediana de SG para a amostra como um todo foi de 11 meses, e o nível mediano de CA 19-9 foi de 542 U/mL. Fatores preditivos de SG em análises univariadas foram o uso de quimioterapia combinada em primeira linha (p=0,006) e o uso de erlotinibe (p=0,002), com nível

de significância limítrofe para nível pré-tratamento de CA 19-9 (p=0,052). Na análise multivariada, apenas o uso de erlotinibe (p=0,003) e o nível pré-tratamento de CA 19-9 (p=0,026) estiveram associados com SG de maneira significativa.

Conclusão. Nosso estudo fornece evidência adicional para o uso do nível pré-tratamento de CA 19-9 como indicador prognóstico e como fator de estratificação em ensaios clínicos. A associação entre uso de erlotinibe e SG pode ter sido devida à seleção de pacientes, não obstante o resultado de um estudo randomizado recente mostrando o benefício desse tratamento.
[Rev Assoc Med Bras 2010; 56(1) 22-6]

Unitermos: Neoplasias pancreáticas.Quimioterapia. Análise multivariada. Análise de sobrevida.

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Artigo recebido: 15/10/08
Aceito para publicação: 29/07/09