Comparison of gemcitabine plus platinum analogue with gemcitabine alone in advanced pancreatic cancer

Eileen O'Reilly and Ghassan Abou-Alfa

A pooled analysis of two randomised trials has shown that gemcitabine in combination with a platinum analogue (cisplatin or oxaliplatin) is a potential front-line treatment option in advanced pancreatic adenocarcinoma.

Treatment for advanced pancreatic adenocarcinoma remains a major therapeutic challenge. In 2008, international standards of care include single-agent gemcitabine, gemcitabine and erlotinib[1] and arguably gemcitabine-based cytotoxic combinations that include a platinum agent or an oral fluoropyrimidine. The pooled analysis performed by Heinemann and colleagues (see opposite) adds to the collective evidence that supports the use of a gemcitabine-based cytotoxic combination in patients with either locally advanced or metastatic pancreatic adenocarcinoma and good performance status.[2]

This pooled analysis combines two important trials conducted in Europe. The French Multidisciplinary Clinical Research Group (GERCOR)/Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) study compared single-agent gemcitabine with a gemcitabine and oxaliplatin combination, while the German multicentre trial investigated the use of a gemcitabine and cisplatin regimen. The summation of data from these trials indicated that combining gemcitabine with either oxaliplatin or cisplatin, enhances progression-free survival (HR 0.75, P=0.0030) and overall survival (HR 0.81, P=0.031) when compared with gemcitabine alone. The benefits associated with combination therapy were most pronounced in patients with a good performance status (HR 0.82, P=0.063).

The pooled analysis overcomes some of the limitations of small individual trials – the conclusions of which can be limited by a lack of statistical power – and is strengthened by assessment of individual data points. Furthermore, the results of this pooled analysis support the well-recognised value of performance status in delineating patient outcomes. Notably, the conclusions are similar to those drawn by Sultana and colleagues in a larger meta-analysis.[2] A potential weakness of the pooled analysis is that the experimental arm included both standard 30 min and fixed-dose rate (protracted infusion) gemcitabine schedules in combination with cisplatin or oxaliplatin. Of note, and somewhat contrary to the conclusions by Heinemann and colleagues, are the preliminary results of the ECOG 6201 trial, which did not suggest a benefit of a gemcitabine–oxaliplatin-based combination over single-agent gemcitabine.[3]

Given the recent disappointing results of phase III trials of gemcitabine in combination with the antivascular agent bevacizumab,[4] or the monoclonal antibody cetuximab[5] (wherein no benefit was noted over single-agent gemcitabine in either study), the relative utility of a cytotoxic combination can be appreciated. Themes are consistent for cytotoxic combinations, with improved response rates, time-to-tumour progression and clinical benefit

Eileen O'Reilly is an associate member, and Ghassan Abou-Alfa is a medical oncologist, at Memorial Sloan-Kettering Cancer Center, and Eileen O'Reilly is an associate professor of medicine, and Ghassan Abou-Alfa is an assistant professor of medicine, at Weill Cornell Medical University, New York, USA. This article was first published online in *Nature Clinical Practice Oncology* on 29 April 2008, and is reproduced with permission. www.nature.com/clinicalpractice, doi:10.1038/ncponc1128 ,

Synopsis

V Heinemann, R Labianca, A Hinke et al. (2007) **Increased survival using platinum analog combined with gemcitabine as compared to single-agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study.** *Ann Oncol 18:1652–1659*

Background. Several randomised trials have demonstrated an improved survival in patients with advanced pancreatic cancer treated with gemcitabine plus a platinum analogue compared with patients treated with single-agent gemcitabine; however, none of these studies has shown a statistically significant survival advantage of combination therapy. It has become clear that trials enrolling larger numbers of patients are needed to prove a statistically significant benefit of therapy with gemcitabine plus a platinum analogue.

Objective. To determine whether treatment with gemcitabine plus platinum results in better overall survival than treatment with single-agent gemcitabine in patients with advanced pancreatic cancer.

Design and intervention. This was a pooled analysis of single-patient data from the French Multidisciplinary Clinical Research Group (GERCOR)/Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) intergroup study (n=326), which compared gemcitabine plus oxaliplatin with gemcitabine, and the German multicentre study (n=195), which compared gemcitabine plus cisplatin with gemcitabine. Both trials had similar inclusion and exclusion criteria and both recruited patients with histologically proven, unresectable, metastatic or locally advanced pancreatic cancer.

Outcome measure. The main outcome measure was overall survival (OS).

Results. Data were available for 503 patients, 252 of whom were treated with gemcitabine plus a platinum analogue and 251 of whom were treated with single-agent gemcitabine. Overall response rates were significantly higher in patients receiving gemcitabine plus a platinum analogue than among those receiving single-agent gemcitabine (22% vs 14%; P=0.028). The median progression-free survival (PFS) for the study population as a whole was 18 weeks. Pooled univariate analysis of PFS revealed a hazard ratio (HR) of 0.75 in favour of combination therapy (P=0.0030). Subgroup analysis revealed that the beneficial effect of the combination regimen on PFS was greater in the group of patients with locally advanced disease than in the group of patients with more widespread disease (35 vs 21 weeks; P=0.051). In addition, among patients with a good performance status, those receiving combined chemotherapy experienced a longer median PFS than patients treated with single-agent gemcitabine (33 vs 14 weeks; P=0.013). Median OS for the whole cohort was 33 weeks, OS was significantly greater in patients receiving combination chemotherapy than in patients receiving gemcitabine alone (HR 0.81, P=0.031). The most important predictors of prognosis were stage of disease (P<0.0001) and performance status (P<0.0001). Subgroup comparisons among patients receiving combination therapy revealed significantly longer OS in patients with good performance status (ECOG status 0) than in patients with more aggressive disease (52 vs 36 weeks; P=0.063).

Conclusion. The results of this pooled analysis reveal that, in comparison with single-agent gemcitabine therapy, treatment with the combination of gemcitabine plus a platinum analogue significantly improves OS and PFS in patients with advanced pancreatic cancer. Combination therapy seems particularly beneficial in patients with a good performance status.

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being relatively constant across studies.

The consistency of these results indicates that in patients with good performance status and symptomatic or bulky disease, a cytotoxic-drug-based combination is a justifiable treatment consideration. It is currently unclear whether two-drug combinations or combinations comprising three or more drugs will confer optimum benefit over gemcitabine. In addition, the extra toxicity incurred from multi-drug combinations needs to be balanced against the potential benefits.

Notwithstanding the modest incremental value of the treatment option suggested by the results of the pooled analysis (i.e. a gemcitabine-based combination), much needs to be done to improve the treatment options for all stages of pancreatic adenocarcinoma. The identification of new active drugs against novel pathways integral to tumour growth and survival is fundamental. An early venture into the 'targeted world' for pancreatic adenocarcinoma, thus far, has been disappointing and, in relative terms, cytotoxic-based combinations are enjoying an indirect re-endorsement. Hence, treatment options in 2008 include single-agent gemcitabine, gemcitabine-based cytotoxic combinations, gemcitabine and erlotinib and, where possible, an emphasis on clinical trial participation.

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