Letter to the Editor

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Trial of Adjuvant Gemcitabine for Pancreatic Cancer: The Jury Is Still Out

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Dear Sir,

A randomized phase III trial of adjuvant gemcitabine following surgical resection of adenocarcinoma of the pancreas has recently been reported [1]. A statistically significant improvement in disease-free survival (the primary endpoint of the study) favouring adjuvant gemcitabine over observation was demonstrated (13.4 vs. 6.9 months, p < 0.001). The authors concluded that the results support the use of gemcitabine as adjuvant chemotherapy in resectable carcinoma of the pancreas. Interestingly, this did not translate into an improvement in overall survival (22.1 vs. 20.2 months, p = 0.06). The authors proposed that this may be due to relative immaturity of the data (although the median follow-up was 53 months) and/or use of palliative chemotherapy for patients in the control arm who subsequently relapsed. However, an alternative explanation for this discrepancy may relate to the trial methodology. The methods used to determine disease recurrence were: (1) assessment of symptoms, and (2) abdominal ultrasound performed 8-weekly. Both of these assessments are subjective. For example, abdominal ultrasound is operator dependent, has limitations in clearly distinguishing local recurrence from post-operative changes and certainly would not detect lung metastases. Furthermore, symptoms of recurrence are frequently non-specific and may initially be mistaken for chemotherapy-related toxicity in the experimental arm, introducing a potential bias into the assessment of recurrence. Thus, these measures are not sufficiently robust to accurately define the primary endpoint of the study and this may provide a further explanation for the absence of a significant difference in overall survival (a more clearly defined endpoint) between the 2 groups despite the apparent doubling of disease-free survival.

Previously, the ESPAC-1 study has demonstrated a statistically significant increase in overall survival with 5-FU-based chemotherapy as an adjuvant to surgical resection of pancreatic cancer [2]. Since gemcitabine is superior to 5-FU in the palliation of advanced pancreatic cancer, it is proposed that it may also be superior in the adjuvant setting. This question has been addressed by the ESPAC-3 study, which is due to report in 2008. In the meantime, based on the data currently available, the role of gemcitabine in the adjuvant setting following resection of pancreatic cancer remains uncertain.

References


Dear Sir,

In reply to the comments of Dr. Palmer on our CONKO 001 study [1], we agree that median disease-free survival is a manifold controversially discussed, relatively weak surrogate parameter for efficacy in adjuvant therapy. In line with this ongoing discussion it has to be realized that symptoms of relapse and interpretation of follow-up investigations are to some extent subjective and principally refer to both groups.

In the CONKO 001 trial, the largest 2-group randomized study evaluating chemotherapy in patients with resected pancreatic cancer, gemcitabine-induced toxicity is very unlikely to have a relevant input, since less than 3% of patients relapsed within the first 6 months; thereafter computed tomography imaging was mandatory. Furthermore, gemcitabine caused a low rate of adverse events with less toxicity compared to 5-FU in the palliative therapy [2].

The primary endpoint of the CONKO 001 study was disease-free survival, and for this parameter the data were mature at the time of the report [1]. Overall survival (OS), a more definite parameter for efficacy, showed a highly suggestive trend (p = 0.06) in the premature intention-to-treat analysis. However, a significant superiority for the gemcitabine arm (median OS: 24.2 vs. 20.5 months, p = 0.02) was observed in the prespecified qualified analysis. From this analysis (147 vs. 164 patients) patients with violations of the entry criteria were excluded as well as those who had not received at least 1 cycle of gemcitabine in the active treatment group and those with prerelapse cytotoxic or radiation therapy in the control group – but patients with early death or early progressive disease in both arms were included.

From a clinician’s view, significant increases in median disease-free survival and median OS are greatly appreciated, but the ultimate parameter for efficacy of postoperative therapy for our patients is improved long-term survival and cure. In the CONKO 001 trial the estimated survival rates [1] of 48 vs. 42%, 34 vs. 21% and 23 vs. 12% after 2, 3 and 5 years, respectively, do favour adjuvant therapy with gemcitabine.

On the other hand, when arguing against the beneficial role of gemcitabine by raising methodological arguments and favouring 5-FU-based adjuvant therapy according to the ESPAC-1 study [2], we do miss a statement by Dr. Palmer regarding the well-known and broadly-discussed limitations of this study including study design, limited statistical power, lack of separate analysis for each of the 4 relatively small groups in the part of ESPAC-1 with a 2 × 2 factorial design.

When discussing the 5-FU versus gemcitabine issue, it is also worth to be stated that the efficacy of gemcitabine is superior to 5-FU in the available head to head comparisons in pancreatic cancer, in palliative therapy [3] as well as in adjuvant chemoradiation [4].

Taken together, today’s scientific evidence recommends adjuvant chemotherapy for patients with pancreatic cancer. The available data do favour gemcitabine over 5-FU in this setting. A detailed study analysis of the CONKO 001 trial, mature now with regard to OS, started recently and will more definitively underline the role of gemcitabine.

References