Drugs 2007; 67 (17): 2491-2493
0012-6667/07/0017-2491/$49.95/0

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Adjuvant Therapy in Pancreatic Cancer: A Critical Appraisal – The Authors' Reply

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We would like to thank Dr Abrams, and Drs Ghaneh, Tudur-Smith and Neoptolemos for their comprehensive and controversial responses to our article.[1] The comments clearly illustrate the difficult situation for all clinicians currently treating patients with resectable pancreatic cancer, i.e. while accumulating evidence from randomised clinical trials supports the usefulness of adjuvant treatment, no generally accepted standard for such treatment exists.

We agree with Dr Abrams[2] that the postoperative radiation programmes used in the GITSG (Gastrointestinal Tumor Study Group), EORTC (European Organisation for Research and Treatment of Cancer) and ESPAC (European Study Group for Pancreatic Cancer)-1 studies do not represent the current standard. Unfortunately, however, no data from randomised studies of chemoradiotherapy using modern radiation strategies in this setting are available apart from RTOG (Radiation Therapy Oncology Group) 9704, and this study did not even try to evaluate the benefit of chemoradiation on its own. As recently shown by Chauffert et al.,[3] in patients with locally unresectable pancreatic cancer, intensive chemoradiotherapy preceding chemotherapy with gemcitabine may even impair survival compared with gemcitabine alone. This was explained by the severe toxicity of the chemoradiation programme that limited subsequent exposure to gemcitabine. Therefore, the simple fact that radiation techniques have been improved recently should not lead radiotherapists to conclude that state-of-the-art radiation is beneficial when given in addition to effective chemotherapy with gemcitabine. Given the high incidence of distant metastasis, even after apparently complete resection of localised pancreatic cancer, this malignancy should be considered a systemic disease that needs to be treated systemically with the most effective agent available. Therefore, it appears logical that any additional local treatment that may adversely affect the systemic antineoplastic activity of gemcitabine should be avoided unless unequivocal evidence emerges from randomised clinical trials that the combined modality is more effective than gemcitabine alone and is associated with an acceptable toxicity.

We also agree with Dr Abrams that it is not possible to draw reliable conclusions from the comparison of survival data from different studies. However, such a comparison may be justified, in the best interest of the patients to be treated, to get an impression of the relative efficacy of two treatment alternatives if no data from direct randomised comparisons are available. Of course, any imbalance in patient baseline characteristics should be considered carefully in this case. Regarding the favourable survival data seen in Charité Onkologie CONKO-001,[4] it is unlikely that they are primarily related to the exclusion of patients with elevated CA19-9 (≥2.5 times the upper limit of normal).

Although this tumour marker was shown to be associated with poor survival in patients with resectable pancreatic cancer,[5] other pretreatment patient characteristics in CONKO-001, including many of those identified by Brennan et al.[6] as significant predictors of survival, were similar to those of ESPAC-1 and RTOG 9704, or even indicated poorer prognosis. For example, 73% of the patients in the observation group of CONKO-001 had positive lymph nodes compared with 65% of those treated with chemoradiotherapy plus fluorouracil (5-FU) in RTOG 9704[7] and 59% of the randomised patients in ESPAC-1.[8]

In response to Ghaneh and colleagues,[9] we cannot and do not fully exclude the possibility that patients may derive some benefit from postoperative 5-FU-based chemotherapy, but neither ESPAC-1 nor the meta-analysis of randomised adjuvant trials by Stocken et al.,[10] which largely reflects the results of ESPAC-1, provide very reliable evidence to support this concept. Although factorial designs are well established in clinical trial methodology, it is also well known that the advantage of increased sample size efficiency is associated with some risk of difficulty in interpretation.[11] These risks do not arise haphazardly; their probability and/or relevance should be assessed in advance, before embarking on a large-scale study. The greatest risk is related to the possibility of an interaction between any of the treatment factors included in the design. Major interactions will render the pooled comparisons inappropriate. Such interactions are particularly predictable if both randomised treatments contain the same drug or if the combined treatment is likely to result in a delay in the administration of one of the single treatments. In the discussion of the main ESPAC-1 publication,[8] it states "the simplest explanation for these observations is that chemoradiotherapy delayed the administration of chemotherapy and consequently reduced the potential benefit of chemotherapy that is derived from delivering it as soon as possible after resection". However, this represents an interaction par excellence, which could have easily been anticipated. As a result, in half of the patients of the chemoradiotherapy (CRT) yes/no comparison this was not a comparison between CRT and no CRT, but more of a comparison between chemotherapy given without any interference compared with chemotherapy given delayed and with its compliance impaired by the toxicity of the preceding treatment. With such obvious risks known from the onset, the ESPAC-1 investigators should have followed the recommendation by the leading methodologists of the Medical Research Council Clinical Trials Unit:[12] "In general, where there is reasonable expectation that two treatments may interact, a factorial design may still be appropriate, but the sample size should be calculated to provide sufficient power for treatment comparisons in subgroups if necessary." Unfortunately, this was not accomplished. Therefore, we share the hope of the ESPAC investigators that ESPAC-3 will provide a clear answer as to which chemotherapy regimen provides optimal outcome in the adjuvant setting.

Acknowledgements

The authors received no funding for preparation of the original review or this commentary. Dr Oettle reports receiving grant support for clinical research projects from the German branches of the following pharmaceutical companies: Amgen, Antisense Therapeutics, Caremark/Fresenius Cabi GmbH, GlaxoSmithKline, Lilly, Logomed, Medac, Merck KG, Novartis, Orion Clinical, Janssen Cilag/Ortho Biotech, Quintiles, Roche Pharma, Sanofi-Aventis and Ribosepharm. Dr Oettle also reports receiving compensation for providing clinical lectures for Lilly and Sanofi-Aventis between 2.5 and 5 years ago. Dr Neuhaus has no conflicts of interest that are directly relevant to the contents of the original article or this reply.

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