Role of second-line chemotherapy in advanced pancreatic cancer and its influence on phase II/III study results

We read with interest the recent report by Rahma et al. [1] on second-line chemotherapy in advanced pancreatic adenocarcinoma. The authors carried out a systematic analysis of second-line studies and found that second-line chemotherapy was associated with a survival advantage when compared with best supportive care. They also suggested that a gemcitabine–platinum combination might be superior to other regimens in this setting.

We carried out a similar analysis with a focus on pooled weighted response rates. Consistent with the authors’ findings, we observed that gemcitabine-based regimens were more active [objective response rate 10.0%; disease control rate (DCR) 54.7%] than fluoropyrimidine-based (7.6%; 32.2%) or taxane-based regimens (5.2%; 33.6%) [2]. Taken together, second-line chemotherapy demonstrates activity but it is unclear whether this translates into survival gain. As the authors correctly pointed out, evidence of chemotherapy benefit over best supportive care is still lacking in this setting.

There is an increasing interest in the role and relevance of second-line chemotherapy in advanced pancreatic cancer, which may have a possible impact on the survival results of first-line studies [4]. We explored the correlation between the percentage of patients who received second-line chemotherapy and reported overall survival in a pooled analysis of first-line phase III and randomised, phase II studies published between 1998 and 2012, using previously described methods [5]. Only studies which reported the percentage of patients receiving second-line chemotherapy were included for analysis. Spearman’s correlation was carried out.

Of 52 studies, only 11 randomised phase II studies (28 arms, n = 1450) and 17 phase III studies (33 arms, n = 5051) reported rates of second-line chemotherapy delivery, which ranged from 14% to 68% (supplementary Table, available at Annals of Oncology online). The percentage of patients who received subsequent chemotherapy significantly correlated with the reported median overall survival [r = 0.49 (0.26–0.67), P < 0.001] (Figure 1). The strength of correlation was improved when only phase III studies were included [r = 0.63 (0.35–0.81), P < 0.001]. On the other hand, the percentage of patients enrolled with either poor performance status [r = 0.03 (−0.24–0.29), P = 0.839] or locally advanced disease [r = 0.13 (−0.14–0.38), P = 0.336] did not correlate with reported overall survival.

While no firm conclusion can be derived from our data, we believe that they add weight to Rahma and colleagues’ support for the use of chemotherapy in the second-line setting for advanced pancreatic adenocarcinoma. Despite promising results from recent studies with FOLFIRINOX and Nab-paclitaxel–gemcitabine, outcomes remain far from optimal. While we fully agree with the authors’ conclusion that future efforts must be focused on individual therapy strategies, we believe that patient outcomes in this disease could also be improved by increasing patient exposure to the available agents. In addition to the search for predictive markers of response, perhaps early predictive markers of therapeutic failure could permit a change in treatment strategy, while the performance status remains uncompromised.

M. Teo* & R. S. McDermott

Department of Medical Oncology, Adelaide & Meath Hospital, incorporating National Children’s Hospital, Tallaght, Dublin 24, Ireland

(*E-mail: neuy924@gmail.com).

disclosure

The authors have declared no conflicts of interest.
Optimizing treatment of seminoma stage IIA/B step by step

We would like to congratulate Horwich et al. for their results on therapy optimization for stage IIA/B testicular seminoma [1]. The 100% recurrence-free survival rate was achieved by the combination of low-intensity carboplatin chemotherapy and partially limited dose and volume radiotherapy. The key idea behind this concept is eliminating the weaknesses of radio- and chemotherapy, if used as single modality. While radiation therapy is highly effective in the paraaortal and pelvic nodal regions, relapses can occur outside the irradiated volume [2]. On the other hand, carboplatin can safely combat microscopic tumour deposits, but it cannot achieve satisfactory remission in the involved lymph nodes [3]. Combining both modalities each in deescalated form can thus achieve optimal results, hopefully without additional toxicity.

The Swiss Group for Clinical Cancer Research (SAKK) together with the German Testicular Cancer Study Group has embarked on a prospective trial to test one cycle carboplatin AUC7 followed by involved node radiotherapy for stage IIA/B seminoma patients (NCT01593241) (http://clinicaltrials.gov/show/NCT01593241). The SAKK-01/10 trial is recruiting patients at nine sites since 2012. The novel approach of the trial is to further deescalate treatment by drastically shrinking the radiation fields to include only the involved lymph nodes and adjacent high-risk regions. A centralized review of initial diagnostic imaging with definition of gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) is carried out upon study inclusion. The CTV, GTV and PTV recommendation by the reference panel is then used by the treating physicians for radiation therapy planning. The resulting PTV as per SAKK-01/10 protocol in a patient with a single affected lymph node is >80% smaller compared with the standard PTV (paraaortal and ipsilateral pelvic lymph node areas) for a seminoma stage IIA/B patient. We expect this reduction in treatment volume to result in a marked difference in the incidence of acute and late adverse events while hopefully maintaining its efficacy.

Early stage Hodgkin’s lymphoma and seminoma are similar diseases with cure achieved in over 90% of patients with first-line treatment. Late treatment sequelae are a major concern, since they may affect even more patients than disease recurrence will. While numerous phase III trials have addressed therapy optimization for all stages of Hodgkin’s lymphoma with practice changing results (http://clinicaltrials.gov/show/NCT01593241), rather little has been done prospectively in seminoma, especially stage IIA/B. One of the problems is surely to obtain appropriate funding for clinical research in this curable and rather rare disease. Therefore, current stage IIA/B seminoma treatment guidelines are based on the retrospective analyses and rather small single-arm prospective trials.

We look forward to joining efforts with interested physicians for collaborative trials on testicular cancer patients testing novel treatment approaches.

A. Papachristofilou1,*, R. Cathomas2, J. Bedke3, R. Souchon4, C. Kolb5 & S. Gillessen6
1Department of Radiation Oncology, University Hospital Basel, Basel, Switzerland
2Department of Medical Oncology, Kantonsspital Graubünden, Chur, Switzerland
3Clinical Trial Management, SAKK CC, Bern
4Department of Medical Oncology, Cantonal Hospital St. Gallen, St Gallen, Switzerland
(*E-mail: alexandros.papachristofilou@usb.ch).

disclosure

The authors have declared no conflicts of interest.

references


doi: 10.1093/annonc/mdt272
Published online 17 July 2013


Dear Sir,

The Bernier [1] proposal regarding specifically the new radio-biodermatitis classification has so far been the only article to