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European Journal of Cancer 41 (2005) 195–196

European Journal of Cancer

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Editorial Comment

# Phase II trials of drug combinations: fairytales or fact?

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Received 9 September 2004; accepted 9 September 2004
Available online 5 November 2004

The problem of designing phase II studies using combinations of drugs or modalities, that each may have their own intrinsic activity, is one that has existed for a long time and is still a matter for debate [1,2]. After careful consideration, the Editorial Board of the *European Journal of Cancer* has agreed upon a policy to not publish non-randomised phase II studies involving combinations, unless the study involves a disease type that is so rare that a randomised study would not be feasible. The current issue of *EJC* exemplifies one of those exceptions. In their paper, ''Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcoma of the bone other than osteosarcoma or malignant fibrous histiocytoma. A European Osteosarcoma Intergroup Study'', Nooij and colleagues [3] report on the outcome of a phase II study using a combination of cisplatin and doxorubicin.

Clearly, these authors have studied a very rare entity. It took this large co-operative group 9.5 years to enter 37 patients. Unfortunately, these 37 patients represent nine different histotypes, three different disease stages and three different performance categories. This renders the number of possible variables almost endless. The authors made the assumption that non-osteosarcomas of the bone would be as sensitive to chemotherapy as osteosarcomas, even though there was no justification for this assumption from previous literature. So what can we learn from this study?

First, we have to compliment the authors, since they have taught us that it is possible to study rare diseases, as long as people are able to join forces. This is the first and most important lesson. The current study calls for a global approach in these rare tumours, rather than pursuing institutional or even national efforts. If studies like these can be extended outside of Europe, we may be able to use designs that are more reliable. The creation of the Connective Tissue Oncology Society (CTOS) some 10 years ago has given us a platform for such world-wide collaboration in the research of mesenchymal malignancies.

Second, the study indicates that these subtypes of bone sarcomas appear to be rather chemo-insensitive, in total contrast to osteosarcomas. Only two of 20 patients that underwent resection after chemotherapy showed a satisfactory histological response to the chemotherapy, and only three of 12 with metastatic disease obtained a short-lasting objective response. Thus, if grouped together, there is no indication that these bone tumours respond favourably to chemotherapy. So if chemotherapy were the subject of future studies in these diseases one could justify the use of a single drug and try to build experience from there. The authors' assumption made before the start of the study with regard to chemosensitivity was therefore wrong. The outcome of their study enables us to start to develop drug treatments for patients with these rare subtypes of bone tumours, but it also teaches us that we should not always base our studies on assumptions. If there are no data available, why not start with a simple one-drug study? But, can we really make this firm statement?

Phase II trials are screening studies. They can generate hypotheses, but their potential should not be overestimated. Further if more than one agent is involved, the problem becomes even more complex. Is the 25% objective remission observed in the current study the result of doxorubicin or cisplatin or of an additive effect of the combination? We will likely never know and are therefore faced with further questions resulting from the study, rather than having been provided with an answer.

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0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2004.09.009

In more common tumour types, one way to solve this problem is by using a randomised phase II trial design, as proposed by the European Organisation for Research and Treatment (EORTC) Protocol Review Committee in 1997 [1]. Of note, the now published trial was initiated before the EORTC PRC made this recommendation, and the EORTC PRC recognised that their recommendation might not apply to very rare diseases. The randomised phase II design does not have the intent for formal comparisons and should not be misused for insufficiently powered trials, but offers protection against possible selection bias. Results can thus be used to design further studies and appropriately estimate numbers [1,2]. An interesting example on how the design can avoid confusion can be found in the proceedings of the 2003 conference of the American Society of Clinical Oncology. There are three abstracts dealing with a platin-based treatment plus the Epithelial Growth Factor Receptor (EFGR)-inhibiting monoclonal antibody, cetuximab, in non-small lung cancer (NSCLC). The first non-randomised study on the combination reports a rather disappointing response rate of 28% with use of gemcitabine and cisplatin [4]. Similar to my suggestion above concerning the EORTC non-osteosarcoma experience that current chemotherapy is not very active in these circumstances, this cetuximab study could lead to the recommendation to stop further development of the agent in combination with platin-based chemotherapy in NSCLC. The second non-randomised study, using the less active chemotherapy combination involving carboplatin and paclitaxel yielded a fascinating response rate of 67% [5]. This would absolutely favour further development. However, how can we be sure that patient selection biases have not influenced the apparently discrepant results? The third study in the same proceedings involved a cisplatin/vinovelbine combination, but randomised patients to this combination or the same combination with the addition of cetuximab. The resultant response rates were 32% and 53%, respectively [6]. While not proving anything yet, the latter results at least create confidence and justification for embarking on a large-scale phase III study, and offers data that can be used for designing that phase III study appropriately. Clearly, the randomised phase II design does not at all replace the randomised phase III study. However, at least the data can be interpreted in such a way that they can be used for further development, something which is difficult if the phase II study is not randomised.

From this perspective, based on the results reported by Nooij and colleagues, we cannot state that combination chemotherapy should not be used in bone sarcomas other than osteosarcoma or the Ewing's family of sarcomas. They may simply by chance have selected a poorly prognostic patient population. So the results of a non-randomised phase II study involving a combination of drugs may be a fairytale, but may also be reality. Since we will never know, this design should only be used after very careful consideration.

## Conflict of interest statement

None declared.

## References

1. No authors listed: Phase II trials in the EORTC. The Protocol Review Committee, the Data Center, the Research and Treatment Division, and the New Drug Development Office. European Organization for Research and Treatment of Cancer. *Eur J Cancer.* 1997, **33**, 1361–1363.
2. Van Glabbeke M, Steward W, Armand JP. Non-randomised phase II trials of drug combinations often meaningless, sometimes misleading. Are there alternative strategies?. *Eur J Cancer* 2002, **38**, 635–638.
3. Nooij MA, Whelan J, Bramwell VHC, Taminiau AT, Cannon S, Hogendoorn PCW, Pringle J, *et al.* Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcoma of bone other than osteosarcoma or malignant fibrous histiocytoma: a European Osteosarcoma Intergroup Study. *Eur J Cancer*, this issue (doi: 10.1016/j.ejca.2004.08.026).
4. Robert F, Blumenschein G, Dicke K, Tseng J, Saleh MN, Needle M. Phase Ib/Iia study of anti-epidermal growth factor receptor antibody cetuximab in combination with gemcitabine/carboplatin in patients with advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2003, **22**, 643.
5. Kelly K, Hanna N, Rosenberg A, Bunn PA, Needle MN. A multicentered phase I/II study of cetuximab in combination with paclitaxel adn carboplatin in untreated patients with stage IV non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2003, **22**, 644.
6. Gatzmeier U, Rosell R, Ramlau R, Robinet G, Szczesna A, Quoiz E, *et al.* Cetuximab in combination with cisplatin/vinorelbine vs cisplatin vinorelbine alone in the first-line treatment of patients with epidermal growth factor receptor positive advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2003, **22**, 642.