Author's response to reviews

Title: Randomized controlled phase I/II study to investigate immune stimulatory effects by low dose radiotherapy in liver metastases of colorectal cancer

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Author's response to reviews: see over
01 August 2011

Dear Mrs. C. Chap

Please find enclosed our revised manuscript entitled “Randomized controlled phase I/II study to investigate immune stimulatory effects by low dose radiotherapy in liver metastases of colorectal cancer” by C. Reissfelder et al., which we submit for review as an article in BMC Cancer.

We are thankful to the reviewer who raised several issues, in particular concerning the statistics.

We are confident that we have addressed and explained these issues satisfactory and in more detail. We would however also like to mention that this trial protocol has been approved by the local IRB and independent local ethical committee of the University Hospital of Heidelberg which included an approval of the statistics. In fact, our statistics have been discussed with and calculated by Dr. Lutz Edler, an experienced biostatistician in the Heidelberg clinical oncology field with many papers in the field including BMC Cancer. In addition, the protocol has been reviewed and funded by a scientific third party funding, which we had not indicated on first submission (grants from Nationales Centrum fuer Tumorerkrankungen (NCT)/Tumorzentrum Heidelberg and Kompetenzverbund Strahlenforschung (KVSF, 03NUK004A,C) of Bundesministerien fuer Bildung, Forschung und Umwelt (BMBF/BMU)). Moreover, a similar protocol with the otherwise very same methods including the statistics has just been published in BMC Cancer (BMC Cancer. 2011 Apr 13;11:134) in patients with pancreatic carcinoma (here: patients with liver metastasis from CRC). Therefore, taken
together, we feel it would perhaps be difficult to change fundamental aspects at this point, if only for ethical reasons.

In General:
While the reviewer mentioned that only a small group of scientists closely related to the field would be interested in our paper, we think that this is not the case. In fact, the potential that a low dose conformal and local radiation with probably very mild side effects, if any, possibly changes the number of active T cells (which is a strong indicator of immunological antitumor effects) should not only cause interest across many oncological fields for scientific reasons, but might have impact on clinical practice and how tumors are irradiated and operated in the future.

Specific:
1. We agree with the review, that the process for the randomization needed to be described in more detail. We have changed this paragraph in the revised version.

2. Dr. Edler’s and the study team’s statistical approach to study group size is based on the assumption that we cannot know a priori the dose response curve between radiation dose and the number of infiltrating T cells in the tumor. In fact, it is not even clear if the curve is linear or nonlinear or even monotonous. It is not impossible, that a U-shaped curve describes the relation. Therefore we chose a wide range of dose (0.5 up to 5 Gy) to “preselect” the dose range which leads to an anti-tumor response at all. The chosen range resulted in part from own animal data (but in another tumor model), which suggest that a dose between 0.5 Gy and 5 Gy to induce an optimal T cell response is needed. On the other hand, the upper limit of 5 Gy is also derived from clinical experience, namely that larger doses than 5 Gy can hardly be considered as having no or minimal side effects. Thus among the radiation doses chosen, the goal was to find the optimal radiation dose for the given tumor entity, which could - in the future - serve as a basis for larger clinical trials. Therefore, a comparison of each treatment group to every other treatment group appeared meaningful. The underlying biology for nonlinear or non monotonous dose response behavior could be, that the response defined as number of tumor infiltrating T-cells is not caused by
a single direct effect of radiation but rather by a combination and interaction of several direct and indirect effects (e.g. via the vasculature, stroma, etc.). It is also possible that higher doses may compromise the beneficial specific immune response, although we do not know clearly where the optimum is. Thus, while one might speculate that up to a certain radiation dose an increasing T cell number is produced, at higher doses the T cell number might be compromised due to many potential effects such as tissue necrosis, perfusion changes, inherent competing immunological effects and so on. In summary, we felt, in order to be on the safe side we concluded that a multiple comparisons comparison would be appropriate.

3. The SDs were judged from the published literature dealing with similar T cell parameters [1,2]. This data from the literature suggested a SD in the range we have used. The SD was also compared with and adapted from data from our own animal experiments (in mice), although the animal model may have artificial components including the fact that many rodents are less sensitive to radiation.

4. The secondary endpoints in this trial are merely exploratory and therefore the statistics are only descriptive. Nevertheless, we agree with the review and changed the statistics paragraph accordingly in the revised version.


Thank you very much for your consideration.
Best personal regards.

Jürgen Weitz