Correspondence

Trans-arterial embolization for hepatocellular carcinoma: doxorubicin is not necessary

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Drs. Cucchetti, Cappelli and Golfieri clearly have an in depth knowledge of the principles and practice of trans-arterial chemoembolization and bland hepatic arterial embolization (HAE) for HCC (1). We appreciate their comments about our recent paper (2) and are grateful for the opportunity to address the concerns raised in their editorial.

With regard to the question of particle size, embolization was begun with 100–300 micron microspheres per protocol in 100 of 101 patients, due to the need for small microspheres to penetrate the intra-tumoral vessels. If stasis was not reached after administering 10 cc of 100–300 micron microspheres the next size—300–500 micron—was used to continue embolization. This, presumably, would result in the smaller spheres penetrating into the most distal and smallest intra-tumoral vessels. By the time 10 cc of 100–300 micron spheres were used it was our hope that the smallest vessels would have been packed with microspheres, allowing the 300–500 micron spheres to fill the larger caliber upstream vessels. This embolization algorithm was then followed with 500–700 and 700–900 micron particles, using a larger size particle only when 10 cc of the smaller size had been used. When additional target vessels were present after completing embolization of the first vessel, embolization was once again begun with 100–300 micron microspheres. The exception was a patient with a 17 cm tumor adjacent to the hemi-diaphragm that was extremely hypervascular with large tortuous vessels and very rapid flow on angiography. These characteristics were thought to place him at very high risk of small microspheres passing through into the systemic circulation (3), leading to a potentially fatal event. Since we have never seen a lung shunt complication with larger particles, embolization began with 300–500 micron spheres. This patient had a CR and remains alive 6 years later.

Larger size microspheres were used in 27 patients during 35 of 212 embolizations (16.5%). Of the 35 embolizations requiring microspheres larger than 100–300 micron, the largest size used was 300–500 micron in 20/212 (9.5%) embolizations, 500–700 micron in 9/212 (4.2%) and 700–900 micron in 6/212 (2.8%) of embolizations. PVA was never used as a tumor embolic agent but only to provide for a standard endpoint. PVA was used on the occasions when continued slow pulsatile arterial flow was noted that prevented achievement of the five beat stasis endpoint but where no tumor vessels were visible, all target vessels were filled with static contrast, and where continued injection of microspheres risked reflux of embolic agent. In these cases stasis was achieved with the smallest amount of 100 micron

PVA, typically less than 0.1 cc. Having championed the use of HAE to treat hypervascular liver tumors for years, and having moved from the age of gelfoam and non-spherical embolics to calibrated microspheres, we are confident that this technique is an appropriate method of causing cell death by inducing tumor ischemia.

Cucchetti *et al.* go on to question whether the groups were really equal. They note that the patients not receiving doxorubicin seemed to suffer from more advanced HCC. Of note, we did not exploit this seeming difference to propose that embolization with microspheres alone might be better than embolization with doxorubicin loaded microspheres. This is because we believe that one needs to define equality of groups very carefully in this context. We know that the populations from which the treatment groups in the trial were drawn were the same, and we randomly assigned the patients to treatments, but the question of whether random assignment produced two groups that were dissimilar with respect to certain characteristics is very difficult to answer statistically. Since all statistical tests attempt to compare the underlying populations, not the observed groups, statistical hypothesis testing cannot help us detect such differences. It was for this reason that we did not present any P values when comparing baseline characteristics; we knew that the underlying populations were the same. For the same reason we are unable to interpret the P values for Okuda stage and portal vein involvement in the editorial. We know that the null hypothesis tested in these comparisons (the populations from which the patients were selected are the same with respect to the characteristic tested) is true. Therefore it is not possible that the P values quoted might represent a Type II error. CONSORT statement (4) and EMEA guidelines (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003639.pdf) strongly discourage these comparisons, as do books on clinical trials (5). A long list of articles in the clinical trial methods literature explains why clinical trials should avoid these comparisons (6-8). We also note that neither of the references cited in the editorial (9,10) deal with comparisons of baseline covariates in randomized trials; in fact Austin (10) strictly deals with propensity-score matched samples, a method used with observational data, so the use of thresholds advocated in these articles, such as an effect size of 0.1, is not appropriate.

Notwithstanding these points, we acknowledge that we pondered the same questions during the analysis of the data. Taking into account the fact that all pre-planned analyses found no statistically significant differences in the protocol-specified outcomes, we decided that although it is possible that the treatment groups were unbalanced with respect to certain characteristics, engaging in a hunt for these characteristics with the hopes of achieving a significant finding between the two groups via a covariate-adjusted analysis in this trial is more likely to yield false positive findings than correct a potential false negative conclusion due to such baseline differences, real or imagined.

Finally, the issue of inclusion criteria was raised. When faced with a word limit in publishing, one must often sacrifice some information in order to include that which is thought to be more important. Suffice it here to say that although patients were permitted to have had previous treatments including surgery, local-regional therapy or chemotherapy, the current tumor burden eligible for treatment on study had to be new or progressing, without previous trans-arterial treatment. The full protocol that describes very clearly the study groups is available on-line through a link in the article and we would encourage those with further questions to have a look.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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