Editorial

Trans-arterial embolization for hepatocellular carcinoma: with or without epidoxorubicin?

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Comment on: Brown KT, Do RK, Gonen M, *et al.* Randomized Trial of Hepatic Artery Embolization for Hepatocellular Carcinoma Using Doxorubicin-Eluting Microspheres Compared With Embolization With Microspheres Alone. J Clin Oncol 2016;34:2046-53.

Submitted Jun 20, 2016. Accepted for publication Jun 24, 2016.
doi: 10.21037/tcr.2016.07.40
View this article at: http://dx.doi.org/10.21037/tcr.2016.07.40

Trans-arterial chemoembolization (TACE) is accepted worldwide as an effective treatment for patients with HCC not candidate for surgery and with a preserved hepatic function. In sharp contrast with the large volume of single-institution experiences with TACE published in the last decades, relatively few randomized controlled trials (RCT) have been reported (1). Considering that TACE represents the most frequent therapy adopted in HCC patients (2,3), high level of evidences are welcome in this setting. In the RCT published by Karen T. Brown in the issue of April of *Journal of Clinical Oncology*, authors tried to verify what is the effect of doxorubicin addition on response and outcome after embolization with microspheres (4). Between December 2007 and April 2012, 51 patients were randomly assigned to receive embolization with Bead-Block (BB) and 50 patients to receive embolization with microspheres loaded with 150 mg of doxorubicin (DEB-TACE). Both arms started the treatment with the same size of microspheres (100–300 μm). Authors did not find any difference in terms of the primary endpoint (radiological tumor response according to the RECIST 1.0 criteria) nor in terms of m-RECIST, safety, progression-free survival or overall survival. Authors concluded that there was no apparent difference between the two treatments questioning the necessity of using doxorubicin.

Early randomized trials, supporting that a survival advantage can be obtained from TACE/bland hepatic embolization (TAE) in respect to best supportive care (BSC), represent the strongest evidence for the adoption of embolization in otherwise non treatable HCC patients. As Authors acknowledge in the introduction section, the RCT from Llovet of 2002, represents the milestone of the superiority of embolization over BSC (5). In this study, 37 patients were assigned to receive TAE, 40 were assigned to receive TACE and 35 were assigned to receive BSC. Bland embolization was performed by injection of gelatin sponge fragments (gelfoam) until flow stasis was achieved and TACE patients received before an emulsion of doxorubicin and lipiodol followed by gelfoam. No difference was observed in median survivals of patients treated with TAE and with TACE, but a significant survival benefit was observed in respect to BSC. Studies like that of Llovet were published during the evolution of the procedure, limiting the value of information obtained in the present clinical scenario with continuous refinement of embolization technique (6).

The optimal size of gelatin sponge fragments for HCC embolization has been reported to be of 0.5–1.0 mm (500–1,000 μm), however, the clinical routine suggests that sizes of about 1–2 mm are most frequently adopted (7). Thus, gelfoam results in more proximal vessel occlusion. The ischemia resulting from embolization is the main factor inducing tumor size reduction but with relative large particles, complete tumor necrosis cannot be achieved. The consequent hypoxia is a strong stimulator of angiogenesis, vital for cancer growth, and embolization can inadvertently promote tumor growth by increasing vascular endothelial growth factor release (8,9). Thus, it is though that smaller

particles can determine more distal vessel occlusion, increasing the complete necrosis achievable and, at the same time, reducing the hypoxic damage. In this sense, embolic agents are consistently evolved during the past decades. On the other hand, HCC is considered a chemo-resistant tumor (10) and to date there is no clear benefit associated with chemotherapy infusion over TAE for HCC treatment. Comparisons of TACE with various chemotherapeutic agents, with TAE have demonstrated neither statistically significant nor clinically meaningful differences in survival in the past (11). As such, the value of chemotherapy infusion as a part of this procedure still remains unclear.

In the study from Brown *et al*. patients received DEB-TACE using LC Bead and TAE using BB. Drug-eluting beads are particles specifically designed to release chemotherapy at a slow rate. Recent studies performed using DEB loaded with doxorubicin has been shown to modify the pharmacokinetics of the injected chemotherapy and, thus, to reduce the drug-related side effects, maintaining the same safety profile and therapeutic efficacy as TACE (12-14). DEB-TACE also showed to have a favorable cost-effectiveness profile (15). BB microspheres can be manufactured with a size similar to that of LC Bead so that are also able to penetrate deeper and to embolize smaller and more peripheral vessels. Being compressible and temporarily deformable, and combined with the product's hydrophilic nature and spherical shape, they can easily smoothly pass through the vasculature (11). In their study, Brown used particles of 100–300 μm as first approach, increasing the diameter of the micro-particles, if stasis was not achieved, up to 500–700 μm for LC beads and up to 700–900 μm for BB (4). This approach lead to a possible final treatment with particles having a diameter similar to that achievable with gelfoam (7) but not data were provided regarding how many patients needed to reach such larger micro-particle size to obtain the stasis. In addition, if after the use of the largest micro-particles the stasis was still not achieved, Authors injected 100 μm of polyvinyl alcohol and it is quite unrealistic to expect a stasis after that a larger diameter was used; instead, what can happen is the reflux of the particle itself.

Apart from such (necessary) technical notes, it can be summarized that the clinical scenario has moved from gelfoam fragments ± doxorubicin of Llovet *et al*. in 2002 (5) toward microspheres ± doxorubicin of the study from Brown of 2016 (4). No clinical survival benefit was observed between the two methodologies in the early past decade and still no survival benefit is observed in the clinical scenario of the present decade.

In the study from Brown *et al*., authors though to isolate the effect that could be ascribed to doxorubicin by assuring that the sole difference in treatment between the two arms was whether the microsphere was loaded with doxorubicin or not. However, this RCT has some limitations deserving discussions. First, were the two groups really equal on the average to support the hypothesis that effect of doxorubicin was isolated? By looking at the first table some doubts may be raised (4). In patients receiving BB, the proportion of Okuda stage II was 23.5% and in patients receiving LC Bead was 14.0%; portal vein involvement in BB patients was present in 25.5% and in patients receiving LC Bead was 12.0%. Thus, patients not receiving doxorubicin seems to suffer from more advanced HCCs. Authors did not attempt for statistical comparison between the two groups but it can be easily calculated for Okuda stage a P=0.309 and for portal vein involvement a P=0.126 (Fisher exact test). The study population was relatively small (51 patients treated with BB and 50 patients treated with LC Beads) and this statistical finding can well represent a type II error, that is the fail to detect an effect that is conversely present. Thus, it would be more informative to assess the effect size of such difference, a measure that is independent from the sample size (16,17). It can be easily calculated that the effect size values for these two tumoral features between the two groups are 0.507 and 0.371, respectively (17). Considering that is commonly though that a negligible difference in terms of effect size can be defined when this value remain below 0.100 (17), it is evident that some unbalance between the two groups is present. However, such features are against patients not receiving doxorubicin, giving the necessary reliability to Author's findings in terms of progression-free and overall survival. Nevertheless, a proper allocation concealment and/or block or stratified randomization, not adopted (or not reported) in the present study, could have increased the average equality of the two groups, giving results additional robustness.

Second, the inclusion criteria are unclear. Authors did not specified in the method section if enrolled patients had a naïve HCC diagnosis, that is, if embolization represented the first line therapy adopted. In the discussion section, they stated that a proportion of patients were already treated with other therapeutic modalities before randomization. The treatment of a recurrence of HCC cannot be compared with the treatment of a first HCC for obvious biological reasons, limiting (again) the consistency of the results. The most reliable result regards the safety profile of TAE and

DEB-TACE. No differences in the number or grade of serious adverse events (SAE), numbers of SAEs per patient, highest grade of SAE were found between the two groups (4) and this finding is undoubtedly independent from the unclear inclusion criteria adopted. The low incidence (11–12%) of SAE after both approaches, confirms that the possibility to avoid doxorubicin to be released outside the tumor can improve the safety of the procedure (14,15).

All in all, even with the methodological limits described that are quite uncommon in the setting of a RCT, the results from the study of Brown raise the following question: why we continue to adopt doxorubicin in combination with embolization? One of the most famous quotes of the U.S. Navy Admiral Grace Murray Hopper during the World War II was that "humans are allergic to change; they love to say that we've always done it this way". Brown results provided partial answer to this dilemma and further RCT, with adequate methodologies and/or with an "effectiveness" aim, are warranted to definitively understand the real need for doxorubicin.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Jian-Hong Zhong (Hepatobiliary Surgery Department, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.07.40). The authors have no conflicts of interest to declare.

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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Cite this article as: Cucchetti A, Cappelli A, Golfieri R. Trans-arterial embolization for hepatocellular carcinoma: with or without epidoxorubicin? Transl Cancer Res 2016;5(S2):S208-S211. doi: 10.21037/tcr.2016.07.40

