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Boris Guiu, Eric Assenat

Editorial Commentary

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Boris Guiu[1], Eric Assenat[2]

[1]Department of Radiology, St-Eloi University Hospital, Montpellier, France; [2]Department of Oncology, St-Eloi University Hospital, Montpellier, France
Correspondence to: Prof. Boris Guiu, MD, PhD. Department of Radiology, St-Eloi University Hospital, 80 avenue Augustin Fliche, 34295 Montpellier, France. Email: B-guiu@chu-montpellier.fr.

Comment on: Abou-Alfa GK, Shi Q, Knox JJ, *et al.* Assessment of Treatment With Sorafenib Plus Doxorubicin vs Sorafenib Alone in Patients With Advanced Hepatocellular Carcinoma: Phase 3 CALGB 80802 Randomized Clinical Trial. JAMA Oncol 2019;5:1582-8.

Submitted Jul 28, 2020. Accepted for publication Aug 10, 2020.
doi: 10.21037/atm-2020-131
View this article at: http://dx.doi.org/10.21037/atm-2020-131

In a recent issue of *JAMA Oncology* (1), Abou-Alfa and colleagues reported no overall survival (OS) and progression-free survival (PFS) benefit with the addition of doxorubicin to sorafenib in patients with advanced hepatocellular carcinoma, in the phase III Alliance/CALGB 80802 trial.

In this open-label trial, 480 patients were supposed to be enrolled. Enrollment began in February 2010, but the trial was stopped in May 2015 on the recommendation of the data and safety monitoring board after the fifth interim analysis showed low probability (futility boundary crossed) that OS in the doxorubicin plus sorafenib group would surpass that in the sorafenib group. Therefore, 356 patients with advanced disease who had received no prior systemic therapy were randomly assigned (1:1) to receive the combination (n=180) of doxorubicin 60 mg/m^2 (30 mg/m^2 in those with bilirubin of 1.3–3.0 mg/dL) every 21 days to a maximum total dose of 360 mg/m^2 plus sorafenib 400 mg twice daily (400 mg once daily in those with bilirubin of 1.3–3.0 mg/dL) or sorafenib alone (n=176). After a median follow-up of 36.1 months, median OS (i.e., the primary endpoint) was reported at 9.3 months in the combination group *vs.* 9.4 months in the sorafenib group (HR, 1.05, 95% CI, 0.83–1.31, P=0.68). Median PFS was 4.0 months *vs.* 3.7 months (HR, 0.93, 95% CI,0.75–1.16, P=0.54). For the sorafenib plus doxorubicin arm, 1 patient achieved a complete response (0.7%) and 14 achieved partial responses (9.3%). For the sorafenib alone arm, no patients achieved a complete response and 8 patients achieved partial responses (5.4%). The response difference was not statistically significant.

Hematologic toxicity, especially grade 3 or 4 neutropenia (36.8% *vs.* 0.6%) and thrombocytopenia (17.5% *vs.* 2.4%), occurred more frequently in the doxorubicin plus sorafenib group than in the sorafenib one. Non-hematologic AEs were comparable in 63.6% and 61.5% of patients respectively, but grade 3 or 4 cardiac toxic events occurred only in the combination group, including left ventricular systolic dysfunction in 3.0% of patients and decreased ejection fraction in 4.8%.

From the CALGB trial, we can conclude that the addition of doxorubicin to sorafenib resulted in higher toxicity and improved neither OS nor PFS. It is interesting to note that the sorafenib median OS of about 10 months was consistent with pivotal studies on sorafenib in HCC, but contrasts with those longer reported in more recent trials (2).

Inhibition of the Ras/Raf/MEK/ERK pathway could prevent the activation of multidrug resistance pathway (3-5), and therefore enhance doxorubicin efficacy against HCC cells. A phase I study assessing the combination of sorafenib with doxorubicin demonstrated a 21% area under the curve (AUC) increase of doxorubicin when both drugs were administered concomitantly (6). This led Abou-Alfa *et al.* to conduct a randomized phase II trial comparing doxorubicin plus sorafenib *vs.* doxorubicin alone in patients with advanced HCC (7). This trial showed greater median time to progression (i.e., the primary endpoint), OS and PFS with respectively 6.4 *vs.* 2.8 months (P=0.02), 13.7 *vs.* 6.5 months (P=0.006) and 6 *vs.* 2.7 months (P=0.006) in the combination group *vs.* doxorubicin alone. The population characteristics, treatment dose and duration in the doxorubicin plus sorafenib group were similar in both trials.

In the CALGB 80802 phase III trial, the authors remind the criticality of phase 3 trials in the setting of promising phase 2 data, but surprisingly the phase 2 trial that led to the phase 3 trial used a different control: doxorubicin instead of sorafenib. Sorafenib was considered as an adjunct treatment to doxorubicin in the phase II trial, under the assumption that it could enhance its efficacy whereas in the phase III, the addition of doxorubicin was supposed to improve the standard of care in advanced HCC.

As such, the CALGB phase III trial adds to the long list of other treatment strategies that have failed to show a superior survival to sorafenib, such as sunitinib in the SUN1170 trial, brivanib in the BRISK-FL trial, erlotinib in the SEARCH trial, linifanib in the LIGHT trial, nivolumab in the CheckMate-459 trial, and radioembolization in the SARAH and SIRveNIB trials.

It is likely that the results observed in the phase II trial were just driven by the sorafenib, not doxorubicin. The authors themselves acknowledged that doxorubicin does not have a role as a systemic therapy for patients with advanced HCC (1). Indeed, the rationale for doxorubicin in HCC treatment is extremely weak. It only relies on a single-arm phase II study conducted in 1975 (8) on 14 HCC patients treated by IV doxorubicin. A tumor response was reported in 11/14 patients, among whom three presented complete response. Of note is that only ultrasonography was available for evaluating tumor response at this time. A case-series published in 1978 reported 32% of clinical remission after treatment by 60 mg/m^2 doxorubicin. The promising results reported in these studies from the 1970s have never been reproduced so far. In addition, only one randomized trial showed a benefit for systemic doxorubicin (over nolatrexed) (9), whereas all the others were negative (10-12). Data coming from studies in the past 40 years clearly show that doxorubicin has very limited activity in HCC.

Even though doxorubicin has never been recommended for systemic treatment of HCC, it remains the main drug used for transarterial chemoembolization (TACE) of HCC. In a recent worldwide survey on HCC TACE, doxorubicin appeared as the most popular cytotoxic agent (71.7% responders) especially in North America, Europe and Korea (13). Yet, its use relies on the same poor rationale than the one previously-mentioned for systemic treatment… This may explain why in many countries, doxorubicin is not approved by health authorities for locoregional treatment of HCC. The randomized trial published by Llovet *et al.* in the Lancet in 2002 (14) demonstrated that TACE (with doxorubicin) improved survival compared to best supportive care. It is important to remember that, in this study, randomization was performed between three groups [TACE, BSC and embolization alone (without any chemotherapeutic agent)]. Unfortunately, the trial was stopped prematurely because TACE was proved superior to BSC, thereby preventing any comparison between TACE (with doxorubicin) and embolization. Interestingly, TACE is the first-line recommended treatment option for BCLC B HCC patients based on the trial by Llovet *et al.* (14) and another one by Lo *et al.* (published the same year) (15) which also demonstrated survival benefit with TACE but using cisplatin, not doxorubicin... This led to call into question the interest of the drug and notably doxorubicin in TACE, as recently highlighted in a randomized phase II trial (again published by the group of Abou-Alfa) showing no difference in terms of response and survival between doxorubicin drug-eluting bead TACE versus bland (i.e., no drug) embolization (16).

This accumulating evidence showing very limited clinical activity of doxorubicin either as systemic treatment or as part of TACE is supported by the results of a screening study showing limited cytotoxicity of doxorubicin on three HCC cell lines (17). From this study, idarubicin exhibited the best cytotoxicity profile, far beyond that of doxorubicin. Phase I and II studies (18-20) on intra-arterial treatment for HCC using idarubicin showed promising efficacy with favorable toxicity profile.

In conclusion, doxorubicin failed to demonstrate any significant clinical efficacy as a systemic treatment for HCC. Additionally, no clear data are available on any efficacy of doxorubicin in TACE. By contrast, a new era begins this year with the positive results of ImBrave 150, reporting a survival benefit of atezolizumab plus bevacizumab versus a 13-year standard of care, namely sorafenib (21). Many combinations of immunotherapies with or without target therapies are under investigation with promising results. After more than 40 years of use despite poor rationale and limited efficacy, it is time to discard doxorubicin for good!

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure from (available at http://dx.doi.org/10.21037/atm-2020-131). The authors have no conflicts of interests 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: Guiu B, Assenat E. Doxorubicin for the treatment of hepatocellular carcinoma: GAME OVER! Ann Transl Med 2020;8(24):1693. doi: 10.21037/atm-2020-131

