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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 38594
Title: Intra-individual comparison of therapeutic responses to vascular disrupting agent C P between rodent primary and secondary liver cancers
Reviewer's code: 00068723
Reviewer's country: Japan
Science editor: Ze-Mao Gong
Date sent for review: 2018-03-06
Date reviewed: 2018-03-08
Review time: 1 Day

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[Y] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The authors investigated vascular damage effects with combretastatin A4 phosphate (CA4P) against rat models of implanted rhabdomyosarcoma (R1) or chemically induced hepatocellular carcinoma (HCC). They found that vascular damage effects were more severe in R1 as compared to HCC. CA4P was applied to R1 and HCC in the same rats. Rationality of this model should be explained. What human situation did this model correspond to? In Introduction, CA4P targets cytoskeletal tubulin of abnormal tumor endothelial cells. How did the authors define abnormal tumor endothelial cells? Were there any differences between abnormal endothelial cells and endothelial cells in healthy tissues? These parts are basis of this study. Human HCC occurs mainly in liver infected with HBV or HCV. The authors analyzed chemically induced HCC. There might be differences in characters between human HCC and this study. How were the

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pathological characters in HCC in this study? Were vascular structures the same as human HCC? This part affects the applicability of this study to human. How to calculate AUC30 should be described. It was hard to imagine AUC30. Figure 2 C and D, Figure 3 C. It was hard to evalualte cell morphology. In addition to the photos, the other ones would be necessary in more magnification.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 38594
Title: Intra-individual comparison of therapeutic responses to vascular disrupting agent C P between rodent primary and secondary liver cancers
Reviewer's code: 01221925
Reviewer's country: Greece
Science editor: Ze-Mao Gong
Date sent for review: 2018-03-06
Date reviewed: 2018-03-10
Review time: 4 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is an interesting paper looking at the effect of a vascular disrupting agent on primary and secondary hepatic tumors in the same animal. Could the authors please respond to the following questions/comments: 1) How were the "36 HCCs created in 14 rats"? Was the distribution deliberate or a matter of chance? 2) Why did the authors choose only up to 12 hrs as a time point, ie how do we know that the action of the vascular disrupting agent does not continue (and even maybe increase) more so over time? 3) It appears that the authors consider the rhabdomyosarcoma as a metastatic lesion. If so, what is the primary? The authors may want to consider that there are primary hepatic rhabdomyosarcomas (although extremely rare). 4) Why were there only male rats used? 5) Regarding the rhabdomyosarcoma, one could argue that there is a different vascularity pattern when we are referring to an "implant" versus a metastatic

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lesion that metastasized through a hematogenous route for example. How would this change the action of the vascular disrupting agent? 5) How do the authors account for the difference in the necrosis pattern between the primary and the metastatic tumor? 6) The authors show a possible different pattern here using an implant of a rare tumor. One could argue that it is not necessarily easy to generalize with other types of metastatic lesions to the liver given the fact that they may follow other routes and other biological behavior.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 38594
Title: Intra-individual comparison of therapeutic responses to vascular disrupting agent C P between rodent primary and secondary liver cancers
Reviewer's code: 00187828
Reviewer's country: Turkey
Science editor: Ze-Mao Gong
Date sent for review: 2018-03-06
Date reviewed: 2018-03-12
Review time: 5 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript entitled "Intra-individual comparison of therapeutic responses to vascular disrupting agent CA4P between rodent primary and secondary liver cancers" has been evaluated. It is a well-written and presented manuscript. The aouthors did extensive work to show the effect of combretastatin-A4-phosphate (CA4P) among hepatocellular carcinomas HCCs). In this particular study, the authors compared therapeutic responses of a vascular-disrupting-agent (VDA) Combretastatin-A4-phosphate (CA4P) among hepatocellular carcinomas (HCCs) and implanted rhabdomyosarcoma (R1) in the same rats by magnetic-resonance-imaging (MRI), microangiography and histopathology. They were able to show that thirty-six HCCs were created by diethylnitrosamine gavaged in 14 rats that were also intrahepatically implanted with one R1 as monitored by T2-/T1-weighted images

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(T2WI/T1WI) on a 3.0T MRI-scanner. Vascular response and tumoral necrosis were detected by dynamic-contrast-enhanced (DCE-) and CE-MRI before, 1h and 12h after CA4P iv at 10 mg/kg (treatment group n=7) or PBS at 1.0 ml/kg (control group n=7). Tumor blood-supply was calculated by a semi-quantitative DCE parameter of area-under-the-time-signal-intensity-curve (AUC30). In vivo MRI findings were verified by postmortem techniques. The authors found that On CE-T1WIs, unlike the negative response in all tumors of control animals, in treatment group CA4P caused rapid extensive vascular shutdown in all R1-tumors, but mildly or spottily in HCCs at 1h. In that tumor necrosis occurred massively in R1-tumors but patchily in HCCs at 12h. AUC30 revealed vascular closure (66%) in R1-tumors at 1h ($P<0.05$), followed by further perfusion decrease at 12h ($P<0.01$); while less significant vascular clogging occurred in HCCs. In conclusion, in this study, they revealed effective performance of CA4P in metastatic over primary liver cancers, leading to future clinical applications of VDAs.