

Peer Review File

Article information: <http://dx.doi.org/10.21037/amj-20-178>.

Comment 1: Mechanism of effect as discussed in early discussion is limited to radiation induced hemorrhagic cystitis (HC). Recommend to add data on why & how HBOT works in chemotherapy induced HC.

Reply 1: Added proposed mechanism of action for how HBOT reduces evidence for reduced urothelial injury in rats receiving HBOT with acrolein instillation, supporting efficacy of HBOT in chemotherapy-induced HC.

Comment 2: Some important details and guidance noted to be missing. After reading this review, audience may like HBOT and be convinced to prescribe it but will have no idea about how long of a therapy is typically required and how quickly can one anticipate to see symptomatic improvement - is it months? Is it one single session? What is the frequency required? Weekly? Monthly?

Reply 2: Added the protocol and results of Dellis et al, in which HBOT was stopped with complete resolution of hematuria – average 32 sessions with range 27 to 44. Also added typical protocols as seen in Villers et al (10 to 40 sessions prescribed initially at 60-120 minutes, one session per day).

Comment 3: Similar lack of any specific information noted in the literature review. Most of the literature cited lacks any specific information with regards to patient characteristics, duration of HBOT treatments and their frequency. In patients who lacked complete response, was there adequate compliance and frequency of HBOT to be comparable with those that did benefit. Any other patient characteristics they noted in their literature review to make this more detailed as opposed to such a superficial 'dive'.

Reply 3: Added discussion regarding adequate compliance and frequency of HBOT. Described that data is limited regarding number of HBOT sessions and the effect on treatment failure. Discussed controversy regarding minimum number of treatments for effect, with comments about the 30 treatment threshold identified by Corman and comparison against patients receiving fewer than 30 treatments in the study performed by Degener. Pointed out the challenge in isolating the effect of number of treatments vs. severity of initial hematuria based on the results of Ribeiro de Oliveira.

Comment 4: In the data mentioning HBOT as primary therapy by Dellis et. al - please indicate if there were any concomitant approaches like hyperhydration or other systemic therapies.

Reply 4: Added that no concomitant approaches were described in the treatment protocol; treatment with surgery or conservative measures only occurred if no benefit

observed on initial treatment, more than 45 treatments required, or severe complications occurred.

Comment 5: Authors mention a single report for HBOT use in children. Is there any data on use in young adults? Any pediatric reports for HBOT in radiation induced HC?

Reply 5: Added further detail to case reports of HBOT used for chemotherapy-induced HC, as well as clarified the paucity of reports for HBOT in isolated radiation-induced HC. Added that most literature on pediatric HC is in the setting of bone marrow transplant, where HC is multifactorial but primarily thought to be caused by chemotherapy and reactivation of BK/adenovirus, with total body irradiation being a lesser contributing factor.

Comment 6: Is age noted to be a risk factor for poor response? Do children or young/younger adults heal faster and hence respond better to HBOT? Does time of HBOT initiation vary for the pediatric age group versus adults?

Reply 6: Age has not been noted to be a significant risk factor for poor response. Added that although Chong et al were able to demonstrate a relationship between age and therapeutic response, they were unable to account for related conditions.

Comment 7: In review of reference 22, line 201, it reads "the amount of blood received is likely a marker of the severity of HC". Is this a conclusion by the authors of the current review or was proposed as an explanation by Oliviera et al? Should be clarified.

Reply 7: Clarified that this is an explanation proposed by Olivera et al, also clarified that the need for transfusion versus no need for transfusion was the primary comparison between resolution and no resolution.

Comment 8: For HC and anticoagulation (mentioned with references 16, 23) - is the conclusion based on patients who continued anticoagulation during hemorrhagic cystitis? I find it difficult to believe that treating physicians would not hold anticoagulation in the presence of frank hematuria and if that is not the case, concomitance of anticoagulation with HC symptomatology and persistence needs to be clarified.

Reply 8: Clarified that these patients received anticoagulation during HC symptomatology, with anticoagulation and antiplatelet therapy being held as soon as possible in the Mouglin et al cohort.

Comment 9: Lines 207 - 215, for the paragraph addressing persistent HC due to underlying malignancy - it will be beneficial to present the patient characteristics

where an underlying malignancy was noted. This is an important warning from this review and should be made more useful by defining some warning signs to be mindful of.

Reply 9: Clarified that for patients with recurrence in the Bevers et al cohort, initial assessment of bladder pathology was noted to be limited by the symptoms of HC at the time of cystoscopy, thus knowing that the initial assessment of malignancy is limited, recurrence is an important consideration should hematuria persist. Added results by Norkool et al, with another warning sign being symptoms which are not adequately managed with conservative measures (i.e. ultimately requiring cystectomy)

Comment 10: Review of references 30 and 31 need more details to go along. What scientific basis were these conclusions based on? Otherwise it seems that the authors are convinced and are briefly just mentioning two references that convinced them - which may not be enough to persuade the audiences of this review.

Reply 10: Added scientific support for why HBOT may in fact reduce angiogenesis in the setting of malignancy. Further elaborated that although results have been mixed, both references ultimately found that the majority of data supported either no effect or an inhibitory effect of HBOT on tumor growth.