| Article details: 2015-0073 | |
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| Title | Effect of unintentional cyclophosphamide under-dosing on diffuse large b-cell lymphoma response – |
| Authors | M. Al-Ahmadi MBBS, A. Lazo-Langner MD MSc, J. Mangel MD, A. Dhalla BSc Phm, K. Liu BSc, L. Minuk |
| **Reviewer 1** | Dr. Caroline Hamm |
| Institution | Windsor Regional Cancer Centre, Medical Oncology, Windsor, Ont. |
| General comments (author response in bold) | 1. Title and Abstract<br>a. Title: Recommend include the word "retrospective review" in the title<br>Retrospective review has been added to the title.<br>b. Abstract: Well done.<br><br>Introduction<br>2. Rationale: The rational for the study is valid. The review of this event that affected over 1000 people living in Ontario is commended. Patients were under-dosed because of a misunderstanding between the manufacturer and centres administering the chemotherapy.<br>3. Objectives: Objectives were clearly stated with valid outcome measurements. Hypothesis stated clearly, but appeared to be biased. Words included in the hypothesis included "minor dose reduction of only one ….. inconsequential"<br>This is a very important comment. We agree that this line implies bias, which was not our intention. The sentence has been deleted. The true goal of the project was more clearly stated in the line that we left in the manuscript: "The goal of this project was to assess the impact (if any) of the cyclophosphamide under-dosing on disease response and clinical outcomes in our patients with DLBCL.<br><br>Methods<br>4. Study design – appropriate<br>5. Setting – Appropriate. Could have been enhanced by including some of the data of the entire patient population affected by this event, including other disease sites at their centre, and all of those in Ontario and New Brunswick affected. There are also learnings that could be shared by explaining exactly how the underdosing occurred. I feel that this should be included. There is a short discussion on page 9, but I feel that this should be expanded upon.<br>**We agree that including all other affected sites in Ontario and the New Brunswick site would have increased the sample size and enhanced the quality of the paper. Our group felt that expanding the study to other sites was not practical. The gain in patient numbers would also have been limited, given that the London site had the largest number of affected patients. Given these reasons, we felt that the results derived from our single site, focusing on one single disease subtype, would still be meaningful.**<br>**An explanation for how the under-dosing occurred is described in detail in the 'Explanation and Comparison with Other Studies' section of the Discussion.**<br>6. Participants: Clearly outlined. Valid way of identification of the case and control group through electronic pharmacy records. Good rationale for choosing this group, as the time to relapse is expected to be within the defined study period in most patients. Controls were well matched by age, International Prognostic Score, type of treatment, any intentional dose reductions, incidence of febrile neutropenia and use of growth factors. I would have like to see included the reason for intentional dose reductions, as some are done at the beginning of chemotherapy because of co-morbidities and age and some are done during chemotherapy because of toxicities.<br>**We did not extract this data from the charts as the treating physician did not always explicitly document why intentional dose reductions occurred.**<br>7. Variables: Table 1 clearly describes the patient characteristics and they are balanced between the two groups. There was a wide variation between the patients in amount of dose reduction in the chemotherapy. Some patients had one cycle dose reduced, some had all cycles affected. For this patient population, the median number of cycles affected was 5, which should be a significant affect as most offer 6 cycles of chemotherapy for this patient population. I would like to see more details on this metric. As well, they do describe that the absolute dilution was not possible to measure but they do offer a reasonable explanation on page 9 of the Discussion. I think this should be moved to the Methods section.<br><br>This data has been incorporated into the results section.<br>Mean Percent of cycles affected for cases 79.5%.<br>Number of patients according to Percent of cycles affected:<br>< 25%: 7<br>25-49%: 5<br>50 -75%: 14<br>>75%: 51<br><br>**As this is an observational paper, the methods section is limited to variables that we controlled, including patient selection, data analysis, and statistics. We feel that the description of the extent of dose reduction fits best in the Discussion section, alongside the explanation of the events leading to this error.** |

8. Data sources / measurement: Standard data extraction was performed. Two assessors blinded to the patient groups assessed defined outcomes.
9. Bias: There seemed to be a bias toward the findings of this study. As stated above, the investigators hypothesized that there would be no difference in the outcome. They state at the bottom of page 9 to 10, that "the motivation of the paper was to provide reassurance to the patients". This is not consistent with an unbiased approach.
**We totally agree. This statement definitely implies bias and was not our intention. The word "reassurance" was replaced with the word "information," to more clearly communicate our true intent.**
10. Study Size: The authors state that they reviewed all cases in their centre that were affected. They do not report the rationale for study size in order to detect a statistically significant difference. (STROBE checklist)[http://www.ncbi.nlm.nih.gov/books/NBK126183/]. They do report a lack of statistical benefit with high p values, yet they don't report what sample size would have been needed to find a statistical difference between these two groups, eg. assuming an affect of 10% in changing outcome in patients. We can always argue that a larger sample size may find a statistical difference. One could suggest that the authors contact the other centres to see if they could collaborate on a publication, yet I would first calculate the required sample size to show a clinically significant benefit before investing in this work.

**A post hoc power analysis indicates that a sample size of 83 patients per group achieves 80% power to detect a 20% difference between groups at the 0.05 level of significance. We did not provide a power calculation in the text as we do not have control over the number of patients affected and there are also methodological issues with this type of post hoc power calculation.**

11. Quantitative variables: N/A
12. Statistical Methods: I would suggest that a biostatistician comment on this part of the article.
a. Statistical methods / control for confounding variables – N/A
b. Methods used to examine subgroups and interactions – N/A
c. Missing data : 4 patients were excluded as they had been lost to followup. They don't report any other missing information.
d. Matching of cases and controls: They do not describe specifically how they identified the controls. I suggest that this be added to the final paper.
**The way in which we identified the controls is described in the first paragraph of the Methods section. Controls were patients treated for DLBCL in our centre over the 2 years preceding the chemotherapy dilution error. They were identified by searching the electronic pharmacy records, and were matched to cases according to stage (limited vs advanced) and by age (+/-5 years).**
e. Sensitivity analysis: not reported.
13. Participants: Well described
14. Descriptive data
a. Well described. See table 1
b. Reported – 4 lost to followup
15. Outcome data
a. There are some limitations to quantification of exposure, as it is impossible to know retrospectively how much dilution occurred in each chemotherapy administration, as the amount of dilution was secondary to an unmeasured "overfill" in each of the bags of saline used to mix the chemo. It would however, be possible to give greater details on the number of the treatments / per cent of treatment that the population of interest was exposed to. They did report median and average, however, I would have like to see more details on this. Also, other authors have been able to calculate dose intensity of chemotherapy in a multi-drug regimen. I believe that this would strengthen this report.
**Given that the absolute dose reduction of cyclophosphamide is unknown, it is not possible to accurately calculate dose intensity. We feel that providing this number based on estimated numbers would be misleading.**
16. Main Results:
a. The cases and controls were matched for most of the important confounders, so there wasn't an adjusted analysis. Eg. Age, intentional dose reductions, International Prognostic Score. This seems appropriate to me. Confidence intervals were not reported which may have offered strength to their conclusions.
**We have consulted with a biostatistician on this matter. The biostatistician informed us that confidence intervals would not be informative in this setting.**
b. Category boundaries: N/A
c. N/A
17. N/A

Discussion
18. Seventy seven analyzable patients at the London Regional Cancer Centre with the diagnosis of diffuse large B cell lymphoma, were exposed to an unintentional lower dose of cyclophosphamide between March 2012 and March 2013. The authors compared their prognostic variables and other important predictive and prognostic factors to a cohort of patients treated two years earlier. They found no difference in progression, nor death between the two groups. There was no difference in overall response rate, nor complete remission rate. There was an appropriate duration of follow-up duration for this disease at 548 days.

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| | 19. Limitations: The sample size is the most obvious limitation of this study. I would agree with the authors that it is highly unlikely that an average of 10% dose reduction in one drug of a multi-drug regimen is likely to affect outcome. That being said, it is important to know what an ideal sample size would be to detect a clinical significant difference in outcome. From the literature we know that a 15% reduction in chemotherapy administration leads to an inferior outcome. [1] It may strengthen the conclusion of the article if the author calculated the relative dose intensity of the chemotherapy administered to patients in their analysis. Documenting a small reduction in dose intensity of chemotherapy administered may help us to understand the results. Perhaps patients in this review received approximately 5% overall reduction in dose intensity of chemotherapy. Calculating this dose reduction would give credence to their conclusions.<br>**The references cited below include patients with other forms of cancer, and the dose reductions in those studies were intentional. In addition, multiple drugs in the multi agent regimen were dose reduced rather than just one drug, like in our case. It is difficult to extrapolate results from studies like these to our situation. A 15% dose reduction in all or most drugs in a regimen may have more of an impact on outcomes than a 10-15% dose reduction in only one drug. It is not our intention for these data to be extrapolated to other malignancies or to other chemotherapy regimens. The implications for the generalizability of our data were somewhat overstated in the paper and will be addressed in the point below (point 20).**<br>20. Bias: The authors also report a bias prior to their investigation. On page 9, they state that the " motivation of this study was to provide reassurance to patients who were affected by this incident". Some of the terminology in the report also implies an opinion which minimizes the risks of the incidence page 4 and 10: "minor dose reduction in 1 drug in a multi-agent chemotherapy may be inconsequential." Regarding the impact of this bias, I do not believe that it affected the results, but dose have an impact on the interpretation of the results in the article.<br>**We recognize that these statements implied bias in our interpretation. This was not our intended message and all of these sentences have now been either removed or edited.**<br>21. I have concerns regarding the interpretation of the data. They have concluded that this data should be used to reassure patients that the under-dosing that they experienced was inconsequential with respect to disease response and risk of relapse. The data set is quite small, there is no rationale reporting for the necessary sample size to detect a clinically significant difference outcomes. They have not attempted to determine the actual dose reduction that the patients received. They state that the patients received on average 10% less cyclophosphamide in a multi-drug regimen. These calculations have been performed in the literature with multi-drug regimens and adequate data supports the need for ideal dosing and adverse outcomes when 15% dose reduction administered intentionally. There is significant literature available that discusses the importance of ideal dosing of chemotherapy. [1,2] As well, strong guidelines that state that underdosing patients who have a high BSA will lead to inferior outcomes. These guidelines are sanctioned by both American Society of Clinical Oncology and Cancer Care Ontario.[3]<br>**This comment is quite true and has been addressed in our response to point 20 above.**<br>22. Generalizability: The authors have also concluded that their findings are generalizable to the rest of the patients that received this dose reduction. There needs to be a more fulsome discussion in this statement as well, as there are many variables such as disease, stage etc. Overall, more information as stated above is needed before this data can be generalized. As a systemic oncology community, we have been working hard to ensure that all patients receive the full ideal dose of chemotherapy. (eg. Obese patients were traditionally under-dosed in the past leading to inferior outcomes). Without a more rigorous analysis of this event, we may inadvertently inappropriately reassure patients and colleagues who are not prescribing / receiving full dose of chemotherapy.<br>**We fully agree that these results are not generalizable to other diseases or chemotherapy regimens. A separate section in the discussion called "limitations" has been added as requested by the editors and it specifically mentions the non-generalizability of our findings. Our original statement regarding generalizability has been removed.**<br>23. Funding : not reported<br>**Our study received no funding.**<br><br>References<br>1. Bonadonna G, Valagussa P, Moliterni A et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. N Engl J Med 1995;332:901-906<br>2. Lepage E, Gisselbrecht C, Haioun C et al. Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients to LNH-87 protocol. Ann Oncol 1993;4:651-656<br>3. Jennifer J. Griggs, Pamela B. Mangu, Holly Anderson, Edward P. Balaban, James J. Dignam, William M. Hryniuk, Vicki A. Morrison, T. May Pini, Carolyn D. Runowicz, Gary L. Rosner, Michelle Shayne, Alex Sparreboom, Lara E. Sucheston and Gary H. LymanAppropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline. JCO May 1, 2012 vol. 30 no. 13 1553-156 |
| **Reviewer 2** | Dr. Darren R Brenner |
| Institution | Alberta health Services, Cancer Epidemiology and Prevention Research |
| General comments (author response in bold) | The authors examine the effects of over-diluted cyclophosphamide and gemcitabine on disease response in patient with diffuse large B cell lymphoma. Patients who received the diluted treatment were matched to a historical group of patients and outcomes including event-free survival, complete remission and overall response rate were considered. The unfortunate mislabelling and resulting over-dilution of cyclophosphamide presents a unique opportunity to study the effects of under- |

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| | dosing on disease response and clinical outcomes. There are, however, a few issues that should be addressed in order for the manuscript to be worthy of publication.<br><br>Major issues:<br>1. In the methods section under study design and participants, it is not clear how the historical group of patients was chosen. Were all patients treated between March 2010 and March 2012 included? Based on age? (1-year groups, 5-year groups)– not clear as there is an imbalance in age. Please expand this section with more detailed information.<br>**The methods section indicates this information. We did not include all patients in the 2 year cohort but matched cases with controls by disease stage (limited vs advanced) and by age based on 5 year groups.**<br>2. The caption for Figure 1 should explain what the 'main study outcome' is. Even though the definition of the main study outcome (event-free survival) is explained in the methods section, it should be explicit throughout the text as well.<br>This was added to the manuscript.<br>**Added to the manuscript**<br>3. Please include the number of progression and death events in Table 1.<br>This was added to the Table 1 as below:<br><br>Chemo underdosing Control P<br>Progression 19 (24.7%) 20 (27.0%) 0.741<br>Death 2 (2.6%) 4 (5.4%) 0.321<br><br>4. Why did the authors not do a secondary analysis of progression and death separately in addition to event-free survival?<br>**There are too few death events during follow up therefore a secondary analysis risks over fitting.**<br>5. Define time of last encounter? – In clinic? The authors did not do a linkage with the Ontario Cancer Registry to examine if any additional events were missed – particularly in the historical cohort (control series)?<br>**The time of last encounter was defined as last clinic visit. This detail has been added to the Methods section.**<br><br>Minor issues:<br>1. Does death mean Cancer-specific mortality or any cause of death? I assume cancer-specific but this is not clarified in the methods.<br>**Mortality in this study is defined as Death from any Cause. This detail was clarified in the Results section.**<br>2. Is this sample size big enough to adequately examine the effects? Some mention of power or sample size should be included – particular when testing hypotheses.<br>**A post hoc power analysis indicates that a sample size of 83 patients per group achieves 80% power to detect a 20% difference between groups at the 0.05 level of significance. We did not provide a power calculation in the text as we do not have control over the number of patients affected and there are also methodological issues with this type of post hoc power calculation.**<br><br>3. The dataset contains a large number of potentially clinically relevant covariates – a strength of the study. The authors should consider a multivariate model including the additional clinical and patient characteristics to strengthen the conclusions from the analyses.<br>**We discussed this with a biostatistician and this is his response: "There is a real risk of over fitting the model. As a rule of thumb, you would need 10 events per explanatory variable. Furthermore, the groups were matched on essential characteristics and there was no difference in these features, so a multivariable model would not provide any more information."**<br>4. Please be consistent throughout the text in terms of writing numbers as digits or in words.<br>**This has been corrected.**<br>5. Please correct grammatical errors throughout. Be aware of tense and voice being used.<br>**This has been corrected.**<br>6. Table 1 - please make sure column 2 is consistent. For the continuous age variable, the (SD) is in column two, whereas it is in column 1 for the other continuous variables). A footnote should be added to explain what statistical test(s) was used to compare the variables in the two groups.<br>**Table 1 has been modified to reflect these comments.**<br>7. In the last two sentences of the first paragraph in the discussion the author states; 'Additionally, the group size is relatively small due to the unique study setting. However, a very similar historical control group provides further reassurance regarding the observed results.' Please expand on this statement with an explanation as to what is meant by similar and how the similarities are reassuring.<br>**We decided to delete these 2 sentences from the paper.** |
| **Reviewer 3** | Dr. Jeffrey A. Bakal |
| Institution | University of Alberta, Canadian VIGOUR Centre, Edmonton, Alta. |
| General comments (author response in bold) | Overall I think the study is well presented.<br>1. For figure 1. The controls and under-dosed group should have the same followup period.<br>The case and control groups have different follow up periods which is reflected in the figure.<br>2. While there are no group differences it might be worth exploring a bit more on patients who did |

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| | have an event, either in all groups and or those who were susceptible to under-dosing.<br>**This is an interesting idea. The number of study patients who had events was small (21 events), though, and there are inherent challenges in trying to analyze small subgroups of patients within studies and drawing conclusions on this level of data.** |