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Research

Effect of unintentional cyclophosphamide underdosing on diffuse large B-cell lymphoma response to chemotherapy: a retrospective review

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Abstract

Background: Between March 2012 and March 2013, a miscommunication in labelling between the drug compounder supplier and cancer centre pharmacies resulted in accidental overdilution of cyclophosphamide and gemcitabine used by several cancer centres in Canada. At our centre, 177 hematology patients were affected, among whom the largest subset of patients was those with diffuse large B-cell lymphoma. In this study, we evaluated the effect of such underdosing on disease response.

Methods: We conducted a retrospective cohort study involving all patients with diffuse large B-cell lymphoma who received at least 1 chemotherapy cycle containing diluted cyclophosphamide at our centre and compared them with a historical group of patients matched by stage and age. The primary outcome was event-free survival (a composite of disease progression or death). Secondary outcomes included complete remission and overall response rate. Groups were compared using unpaired Student *t*, χ^2 or Fisher exact tests, as appropriate. Survival analysis was done using the Kaplan–Meier method.

Results: Event-free survival was no different between groups (log-rank $p = 0.99$). At a median follow-up of 548 days, progression or death occurred in 21 of 77 patients in the case group (27.3%) and in 24 of 74 patients in the control group (32.4%) ($p = 0.5$). At the end of treatment, complete remission was achieved in 41 patients in the case group (53.2%) and 43 patients in the control group (57.3%) ($p = 0.6$), whereas overall response rate was 71.4% in the case group and 66.7% in the control group ($p = 0.5$).

Interpretation: Compared with a historical control group, we found no differences in event-free survival or response rates among patients with diffuse large B-cell lymphoma who received 1 or more doses of accidentally diluted cyclophosphamide-containing chemotherapy.

Cyclophosphamide and gemcitabine are key components of several chemotherapeutic regimens used to treat many malignant diseases, including non-Hodgkin lymphoma and breast cancer. In March 2013, it was discovered that a labelling miscommunication between the drug compounder source and hospital pharmacies resulted in overdilution and consequently unintentional underdosing of gemcitabine and cyclophosphamide in several cancer centres in Ontario and New Brunswick. The exact extent of the underdosing is unknown, but based on the dilution error, it is estimated that it could have resulted in a dose reduction of between 3% and 20%.[1,2] Overall, between March 2012 and March 2013, 1202 cancer patients received diluted chemotherapy. At our institution, 177 hematology patients were affected, most of whom were receiving treatment for non-Hodgkin lymphoma,[3] with the largest subgroup being those with diffuse large B-cell lymphoma.

This situation understandably created a great deal of anxiety and uncertainty among affected patients and their physicians. Although dose reduction is a common practice in patients experiencing adverse effects of chemotherapy, there is little information on the potential effect such reductions might have on the response rate in these patients. Such data are necessary to provide reassurance to patients, and to guide further management decisions. Therefore, the goal of this project was to assess the impact (if any) of the cyclophosphamide underdosing on disease response and clinical outcomes in our patients with diffuse large B-cell lymphoma (the largest group affected among hematology patients).

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Methods

Study design and participants

We conducted a retrospective cohort study at the London Regional Cancer Program (London, Ontario), including all consecutive patients receiving treatment for newly diagnosed diffuse large B-cell lymphoma with a first-line cyclophosphamide-containing regimen between March 2012 and March 2013, which was the period of time during which patients received diluted doses of cyclophosphamide. Patients were identified by searching the electronic pharmacy records. To compare response and survival rates, the cohort was compared with a historical group of patients with diffuse large B-cell lymphoma who had received treatment during the 2 years preceding the underdosing error. Patients in the case and control groups were matched for disease stage and age (± 5 yr). Patients in both groups were excluded if they had received previous treatment for lymphoma. Data were extracted from charts using standardized case report forms. Data included patient demographics, lymphoma histology, stage, international prognostic index,[4] chemotherapy regimen, number of cycles of chemotherapy given, any intentional dose reductions, infectious complications and febrile neutropenia rate, and other relevant clinical and laboratory variables. The time of last encounter was defined as the last follow-up in clinic for the purpose of calculating median follow-up. The study was approved by the Research Ethics Board at the University of Western Ontario (London, Ontario).

Study outcomes

The main outcome was event-free survival, defined as a composite of disease progression or death from the time of first chemotherapy. Secondary outcomes were overall and complete response rates. Disease response was assessed by the Cheson criteria.[5] Outcomes were adjudicated independently by 2 assessors blinded to the patient group based on clinical, radiologic and pathologic assessments, as appropriate. Discrepancies were resolved by consensus with a third adjudicator.

Statistical analysis

Baseline characteristics of the groups were described using central tendency measures. Continuous variables were compared between groups using unpaired Student *t* tests. Categorical variables were compared using χ^2 or Fisher exact tests. Survival analysis was done using the Kaplan–Meier method. Patients were censored at the time of the last encounter. Groups were compared using the log-rank test. We considered *p* values of less than 0.05 significant. All analyses were conducted using SPSS Statistics 20.

Results

Patient characteristics

Between March 2012 and March 2013, 81 patients with newly diagnosed diffuse large B-cell lymphoma received 1 or more doses of diluted cyclophosphamide during their treatments. Four patients were excluded because of loss to follow-up. The study group was compared with 74 matched historical control patients. There were no differences in the baseline characteristics between groups (Table 1). About half of the patients were male, and the mean age was 65 years. Most of the patients were given a combination of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab. The median number of cycles affected by the cyclophosphamide dilution was 5 (interquartile range 1–8), which on average represented 79.5% (SD 28.6) of chemotherapy cycles. The number of patients affected according to the percent of cycles affected were as follows: < 25% of cycles affected — 7 patients; 25%–49% of cycles affected — 5 patients; 50%–75% of cycles affected — 14 patients; > 75% of cycles affected — 51 patients. There was no significant difference in the proportion of patients with febrile neutropenia, needing chemotherapy dose reduction, or with the need to use granulocytes colony-stimulating factor.

Outcomes

Survival analysis showed no difference in the main outcome (event-free survival) at a median follow-up of 548 days (log-rank $p = 0.999$) (Figure 1). At the last follow-up, progression or death from any cause occurred in 21 (27.3%) patients in the case group and 24 (32.4%) patients in the control group ($p = 0.5$). Subgroup analyses did not find a difference in the main outcome in patients in whom more than 50% of the chemotherapy cycles were affected by underdosing. At the completion of the treatment, an overall response was achieved in 55 (71.4%) patients in the case group and 50 (66.7%) patients in the control group ($p = 0.5$), whereas complete remission was observed in 41 (53.2%) patients in the case group and 43 (57.3%) patients in the control ($p = 0.6$).

Discussion

This study shows that the response rate and event-free survival was not affected in a group of patients with diffuse large B-cell lymphoma affected by a minor reduction in the dose of cyclophosphamide compared with a historical control group.

Medication errors in chemotherapy drugs may result in substantial adverse events owing to the low therapeutic indices and high toxicity of these drugs.[6] Such errors are not an uncommon problem in cancer centres, with reports showing 7000 patients deaths and 80 000 admissions to hospital annually in the United States,[7] with similar results reported in Canada.[8] Errors may occur at any stage of the treatment process, from prescribing to administration. In a single-centre prospective study, 141 chemotherapy medication errors occurred during the 2-year study period, resulting in an error rate of 0.04% of all medication administrations. Of these, 21% were order writing and transcribing errors, 38% were nurse or pharmacy dispensing errors, and 41% were nurse administration errors. Only 3 errors resulted in adverse drug events.[9]

The sequence of events leading to the chemotherapy underdosing in our study was the subject of a government investigation by the Ontario Ministry of Health and Long-term Care (the Thiessen report).[1,3] The underdosing in our jurisdiction occurred after multiple hospitals changed their supplier of gemcitabine and cyclophosphamide. These cancer centres receive

stock solution of chemotherapeutic drugs at a set concentration from the compounding pharmacy and then use this stock solution to prepare individual doses for multiple patients. The exact nature of the dilution error is best described by the Thiessen[1] report as follows:

> MHS (name of the drug supplier) employed a process in the preparation of the bulk reconstituted cyclophosphamide and gemcitabine that failed to compensate adequately for an overfill factor in the supplier's normal saline bags. On the basis of the MHS labels on the bags (4000 mg per 100 mL bag for gemcitabine; 4000 mg per 200 mL bag for cyclophosphamide), the best estimate is that the average actual cyclophosphamide concentration was 10% lower than that stated on the label. For gemcitabine the average actual concentration was 7% lower than stated on the label. In the absence of clarifying patient-related instructions by MHS to the hospitals, the hospitals were not aware of the need to adjust doses accordingly to factor in the aforementioned lower concentrations. Thus, the overfill issue led directly to the patients under-dosing for both gemcitabine and cyclophosphamide.

By the time this error was discovered, more than 1200 patients in 4 cancer centres had already been given the incorrectly prepared drugs.

Limitations

A potential limitation of our study is that the median follow-up was relatively short, although we feel it is still meaningful given that most relapses of diffuse large B-cell lymphoma occur within the first 2 years of treatment.[10] We plan to continue following this group for a longer period to see if there is an increased risk of late relapses. In addition, the number of patients affected is too small to definitively conclude that this dose reduction in cyclophosphamide had no effect on outcomes. Finally, a substantial limitation is that the exact extent of chemotherapy dose reduction is unknown. We estimated the overall reduction based on the chemotherapy preparation error, but the exact exposure for each individual patient is unclear.

Table 1: Baseline characteristics of the study population

Characteristic	Patients affected by chemotherapy underdosing, no. (%)* $n = 77$	Control group, no. (%)* $n = 74$	p value
Male sex	39 (52)	36 (48)	0.9
Age, mean ± SD, yr	77 ± 16	66 ± 14	0.7
Age > 60 yr	29 (37.7)	24 (32.4)	0.5
LDH, mean ± SD	408 ± 375	394 ± 50	0.8
WBC, mean ± SD	8.2 ± 4	7.5 ± 3	0.2
Hemoglobin, g/L, mean ± SD	117 ± 22	120 ± 21	0.4
Platelets × 10^9/L, mean ± SD	259 ± 175	253 ± 128	0.8
Extranodal site involvement > 1	18 (23.4)	18 (24.3)	0.9
Stage III/IV	53 (68.9)	51 (68.8)	0.99
B symptoms†	44 (57.1)	43 (49.4)	0.8
ECOG ≥ 2	33 (42.9)	36 (49.3)	0.4
Elevated LDH	52 (67.5)	43 (58.1)	0.2
High risk (R-IPI score of ≥ 3)	27 (35.1)	28 (37.8)	0.5
CHOP-R-based chemotherapy	71(92.2)	68 (91.9)	0.9
Prescribed (intentional) dose reduction	23 (30)	25 (34.7)	0.5
Radiotherapy	33 (42.9)	34 (46.6)	0.5
Febrile neutropenia	21 (27.3)	15 (20.3)	0.3
G-CSF use	48 (62.3)	38 (53.5)	0.3
Progression	19 (24.7)	20 (27.0)	0.7
Death	2 (2.6)	4 (5.4)	0.3

Note: CHOP-R = cyclophosphamide adriamycin, vincristine, prednisone, rituximab; ECOG = Eastern Cooperative Oncology Group, G-CSF = granulocytes colony-stimulating factor, LDH = lactate dehydrogenase, R-IPI = revised international prognostic index, WBC = white blood cells.
*Unless otherwise specified.
†Fever greater than 38°C, night sweats, unintentional weight loss of more than 10% body weight over 6 or fewer months.

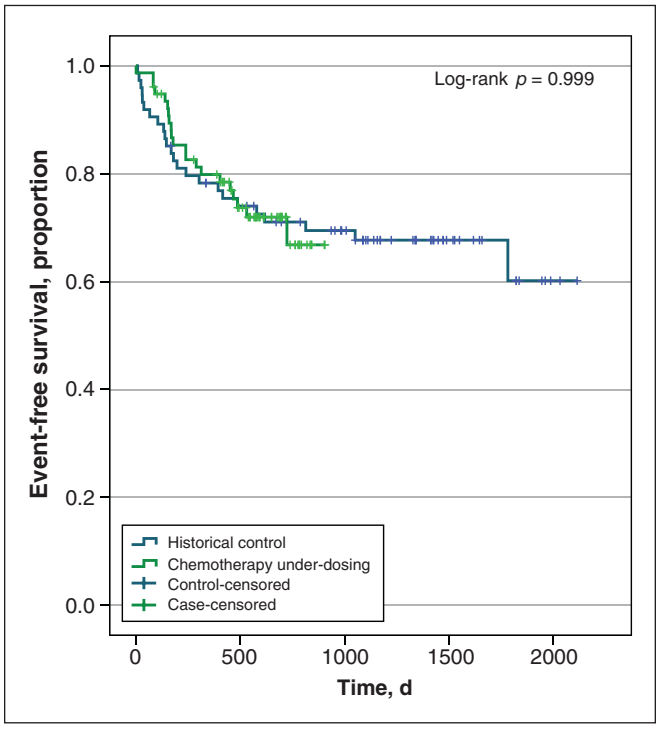

Figure 1: Kaplan–Meier plot for the main study outcome, event-free survival, defined as a composite of disease progression or death from the time of first chemotherapy. Patients were censored at the time of last follow-up.

Conclusion

Patients affected by this event felt a great deal of anxiety and uncertainty in regards to the impact this error may have had on their treatment outcomes. The lack of existing evidence made it difficult for physicians to counsel their patients appropriately. Therefore, the motivation for doing this study was to provide information to the patients who were affected by this incident, as well as to the medical community at large. We chose diffuse large B-cell lymphoma because it is an aggressive neoplasm for which disease response and survival can be assessed in a relatively short period of time unlike indolent lymphomas or breast cancer, the latter being the largest group affected by the dilution error. Our data showed no significant difference in the response rate or in event-free survival among patients receiving 1 or more doses of accidentally diluted cyclophosphamide, compared with a matched historical control group. This information may provide reassurance to patients and their physicians affected by this dosing error. We cannot, however, extrapolate these data to cancers other than diffuse large B-cell lymphoma or to the patients affected by gemcitabine underdosing. The effect on these patient populations will require further study.

References

1. Thiessen J. *A review of the oncology under-dosing incident: a report to the Ontario Minister of Health and Long-Term Care*. Queen's Printer of Ontario; 2013. Available: www.health.gov.on.ca/en/public/programs/cancer/drugsupply/docs/report_thiessen_oncology_under-dosing.pdf (accessed 2015 June 9).
2. Andreatta D. Dilution of chemo drugs was result of 'gaps in communication,' report says. *The Globe and Mail* [Toronto]. 2013 Aug. 7. Available: www.theglobeandmail.com/news/national/health-canada-should-regulate-chemotherapy-services-review/article13630197/ (accessed 2015 June 9).
3. *Standing Committee on Social Policy: diluted chemotherapy drugs* [2nd Session, 40th Parliament]; Toronto: Legislative Assembly of Ontario; 2014. Available: www.ontla.on.ca/committee-proceedings/committee-reports/files_html/40_2_SP_DilutedChemo_01042014_en.htm (accessed 2015 June 9).
4. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007;109:1857-61.
5. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;32:3059-68.
6. Ulas A, Silay K, Akinci S, et al. Medication errors in chemotherapy preparation and administration: a survey conducted among oncology nurses in Turkey. *Asian Pac J Cancer Prev* 2015;16:1699-705.
7. Kohn LT, Corrigan JM, Donaldson MS, editors. *To err is human: building a safer health system*. Washington: National Academy Press; 2000.
8. Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ* 2004;170:1678-86.
9. Ford CD, Killebrew J, Fugitt P, et al. Study of medication errors on a community hospital oncology ward. *J Oncol Pract* 2006;2:149-54.
10. Maurer MJ, Ghesquieres H, Jais JP, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol* 2014;32:1066-73.

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Contribution: A. Lazo-Langner, J. Mangel and L. Minuk designed the study; M. Al-Ahmadi, A. Dhalla and K. Liu collected the data; A. Lazo-Langner and M. Al-Ahmadi analyzed the data; M. Al-Ahmadi wrote the first draft of the manuscript; L. Minuk, A. Lazo-Langner and J. Mangel edited the manuscript. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors approved the final version of the manuscript to be published and agree to act as guarantors of the work.

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