Effect of Unintentional Cyclophosphamide Under-dosing on Diffuse Large B-Cell Lymphoma Response

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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 over-dilution of cyclophosphamide and gemcitabine utilized by several cancer centers 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 (DLBCL). In this study, we evaluated the effect of such under-dosing on disease response.

Methods: We conducted a retrospective cohort study of all patients with DLBCL who received at least one chemotherapy cycle containing diluted cyclophosphamide at our centre and compared them to a historical group of patients matched by stage and age. The primary study 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's t-test, Chi-squared or Fisher's 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=0.999). At a median follow up of 548 days, progression or death occurred in 21/77 cases (27.3%) and 24/74 controls (32%) (P= 0.523). At the end of treatment, complete remission was achieved in 41 cases (53.2%) and 43 controls (57.3%) (P= 0.612) whereas overall response rate was 71.4% in cases and 66.7% in controls (P=0.525).

Conclusions: Compared to a historical control group, we found no differences in event-free survival or response rates among DLBCL patients who received one or more doses of accidentally diluted cyclophosphamide-containing chemotherapy.

Introduction

Cyclophosphamide and gemcitabine are key components of several chemotherapeutic regimens used to treat many malignancies including non-Hodgkin's lymphoma and breast cancer. In March 2013, it was discovered that a labelling miscommunication between the drug compounder source and hospital pharmacies resulted in over-dilution and consequently unintentional under-dosing of gemcitabine and cyclophosphamide in several cancer centres in Ontario and New Brunswick. The exact extent of the under-dosing is unknown, but based on the dilution error, it is estimated that it could have resulted in a dose reduction anywhere 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, the majority of whom were being treated for non-Hodgkin's lymphoma (3), with the largest subgroup being those with diffuse large B cell lymphoma (DLBCL).

This situation understandably created a great deal of anxiety and uncertainty amongst affected patients and their physicians. While dose reduction is a common practice in patients experiencing side effects of chemotherapy, there is little information on the potential effect such reductions might have on the response rate in these patients. Such data is necessary in order 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 under-dosing on disease response and clinical outcomes in our patients with DLBCL (the largest group affected among hematology patients).Our hypothesis was that a minor dose reduction of only 1 drug in a multi-agent chemotherapy regimen was likely to be inconsequential in terms of disease response.

Methods

Study design and participants

We conducted a retrospective cohort study at the London Regional Cancer Program (London, Ontario, Canada), including all consecutive patients treated for a newly diagnosed DLBCL 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. In order to compare response and survival rates, the cohort was compared with a historical group of patients with DLBCL treated during the 2 years preceding the under-dosing error. Patients and controls were matched for disease stage, and age (+/- 5 years). Patients in both groups were excluded if they had received previous treatment for lymphoma. Data was 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/febrile neutropenia rate, and other relevant clinical and laboratory variables. The study was approved by the Research Ethics Board at the University of Western 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 two assessors blinded to the patient group

based on clinical, radiological, and pathological assessments, as appropriate. Discrepancies were resolved by consensus with a third adjudicator.

Statistical analysis

Baseline characteristics of the groups were described by using central tendency measures. Continuous variables were compared between groups using unpaired Student's t-tests. Categorical variables were compared using Chi-squared or Fisher's 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. P-values< 0.05 were considered as statistically significant. All analyses were conducted using SPSS Statistics 20 (IBM Corp. Armonk, NY, USA)

Results

Patients' characteristics

Between March 2012 and March 2013, eighty-one patients newly diagnosed with DLBCL received one 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 controls. There were no differences in the baseline characteristics between groups (**Table 1)**. Approximately half of the patients were male and the mean age was 65 years. The majority of the patients were treated with a combination of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab. The median number of cycles affected the by the cyclophosphamide dilution was 5 (interquartile range 1 to 8) which on average represented 79.5% (SD 28.6) of chemotherapy cycles. There was no statistically significant difference in the proportion of patients developing febrile neutropenia, needing chemotherapy dose reduction, or the need to use granulocytes colony stimulating factor (G-CSF).

Study Outcomes

Survival analysis showed no difference in the main outcome at a median follow up of 548 days (log-rank P=0.999) (**Figure1**). At the last follow up, progression or death occurred in 21 (27.3%) cases and 24 (32%) controls (P= 0.523). 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 under-dosing. At the completion of the treatment, an overall response was achieved in 55 (71.4%) cases and 50 (66.7%) controls (p=0.525) whereas complete remission was observed in 41 (53.2%) cases and 43 (57.3%) controls (p= 0.612).

Discussion

The present study shows that the response rate and event-free survival was not affected in a group of DLBCL patients affected by a minor reduction in the dose of cyclophosphamide compared to a historical control group. A potential limitation of our study is that the median follow up was relatively short although we feel is still meaningful given that most relapses of DLBCL occur within the first 2 years of treatment. We plan to continue following this group for a longer period of time. 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.

Medication errors in chemotherapy drugs may result in significant adverse events due to their low therapeutic indices and high toxicity(6). Such errors are not an uncommon problem in cancer centers, with reports showing 7000 patients deaths and 80,000 hospitalizations annually in the United States (7), and similar results are 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 two-year study period, resulting in an error rate of 0.04% of all medication administrations. Twenty-one percent of these were order writing and transcribing errors, 38% were nurse or pharmacy dispensing errors, and 41% were nurse administration errors. Only three errors resulted in adverse drug events (9).

The sequence of events leading to the chemotherapy under-dosing 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 under-dosing 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 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, over 1200 patients in 4 cancer centres had already been treated with the incorrectly prepared drugs.

Patients affected by this event experienced 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 council their patients appropriately. Therefore, the motivation for doing this study was to provide reassurance 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 statistically significant difference in the response rate or in event-free survival among DLBCL patients receiving one or more doses of accidentally diluted cyclophosphamide, compared to a matched historical control group. This suggests that a minor dose reduction in 1 drug in multi-agent chemotherapy may be inconsequential in terms of disease response and risk of relapse, and although we cannot conclude anything for the other groups of affected patients, it would be reasonable to speculate that such patients would not have had an impact on disease response derived from the accidental chemotherapy under-dosing. We believe that this data should provide reassurance to the affected patients and their physicians.

Authorship:

Contribution: A.L-L, JM and LM designed the study; MA, AD and KL collected the data; A.L-L and MA analyzed the data; MA wrote the first draft of the manuscript; LM, A. L-L, JM 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.

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Figure 1. Kaplan – Meier plot for the main study outcome

Figure 1 footnote. Patients were censored at the time of last follow up.

Table.1 Baseline characteristics of the study population

	Patients affected by chemotherapy under-dosing N=77	Historical Controls N= 74	P value
Male [N (%)]	39 (52)	36 (48)	0.87
Age (Mean)	77 (SD ± 16)	66 (SD±14)	0.67
Age > 60 years [N (%)]	29 (37.7)	24 (32.4)	0.50
LDH [Mean (SD)]	408 (375)	394 (50)	0.82
WBC [Mean (SD)]	8.2 (4)	7.5 (3)	0.19
Hemoglobin g/L[Mean (SD)]	117 (22)	120 (21)	0.35
Platelets x 10^9/L[Mean (SD)]	259 (175)	253 (128)	0.82
Extra-nodal site involvement> 1 [N (%)]	18 (23.4)	18 (24.3)	0.89
Stage III/IV [N (%)]	53 (68.9)	51 (68.8)	0.99
B-symptoms [N (%)]	44 (57.1)	43 (49.4)	0.83
ECOG ≥ 2 [N (%)]	33 (42.9)	36 (49.3)	0.40
Elevated LDH [N (%)]	52 (67.5)	43 (58.1)	0.23
High risk (R-IPI of score ≥3) [N (%)]	27 (35.1)	28 (37.8)	0.50
CHOP-R-based chemotherapy	71(92.2)	68 (91.9)	0.94
Prescribed (intentional) dose reduction [N (%)]	23 (30)	25 (34.7)	0.52
Radiation therapy [N (%)]	33 (42.9)	34 (46.6)	0.53
Febrile neutropenia [N (%)]	21 (27.3)	15 (20.3)	0.31
G-CSF use [N (%)]	48 (62.3)	38 (53.5)	0.28

Abbreviations: LDH: Lactate dehydrogenase, WBC: White blood cells, G-CSF: Granulocytes colony stimulating factor. ECOG: Eastern Cooperative Onvology Group, R-IPI: Revised International Prognostic Index, CHOP-R: cyclophosphamide adriamycin, vincristine, prednisone, rituximab