Relative dose intensity of systemic chemotherapy in an outpatient cancer center

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Objective. This study was undertaken to determine the average relative dose intensity (RDI) of chemotherapy administered to patients in a community-based outpatient cancer center. **Methods.** A retrospective review of medical records in an outpatient cancer center was conducted for patients initiating systemic chemotherapy in 2007 for a diagnosis of lymphoma, breast, lung, ovary, or colon cancer. Eighty-four records meeting the inclusion criteria were reviewed for demographic information, primary tumor type, chemotherapy regimen, staging at diagnosis, presence of disease progression, and mortality status. Regimen data included: chemotherapeutic agents used, dosages administered, dates of administration, treatment intent (adjuvant vs. metastatic), and granulocyte colony-stimulating factor (G-CSF) usage per cycle. Mean summary statistics were calculated and average RDI was analyzed. **Results**. The overall RDI at our institution was 83% (n=65). The RDI for those receiving adjuvant chemotherapy was 85% (n=51), whereas for those receiving chemotherapy for metastatic disease the RDI was 76% (n=14). Fifty-four percent (n=35) of the regimens met or exceeded the recommended minimum goal RDI of ≥ 85%. **Conclusions**. Overall the average RDI at our institution was 83%, slightly below the goal of ≥ 85%. Patients with potentially curable malignancies receiving adjuvant chemotherapy reached the threshold RDI; however, areas for quality improvement exist at our institution.

Key Words: Drug therapy, Chemotherapy, Dose intensity.

Introduction

Dose intensity (DI) is defined as the total amount of drug delivered to a patient over the total time course of treatment (1). Relative dose intensity (RDI) is the ratio of the dose intensity delivered to the reference standard dose intensity for a chemotherapy regimen (2). Retrospective analyses of randomized controlled clinical trials have suggested a strong association between RDI and disease-free and overall survival, especially for lymphoma and cancers of the breast, lung, ovary, and colon (2-13). In particular, data show increased survival for patients receiving greater than or equal to 85% RDI

and conversely, mortality curves similar to untreated populations when this threshold RDI was not administered (11-13). Reductions in chemotherapy dose intensity through dose reductions and/or delays may potentially compromise disease control and survival in patients with curable malignancies (2, 3). The primary objective of this study was to determine retrospectively the average RDI of chemotherapy administered to patients in an outpatient cancer center. In addition, the RDI was separately determined for patients receiving adjuvant chemotherapy and chemotherapy for metastatic disease.

Methods

Study design, setting, and population

A retrospective review was conducted of medical records in a community-based outpatient cancer center. Medical records were reviewed for patients initiating systemic chemotherapy in 2007 for a diagnosis of lymphoma or cancer of the breast, lung, ovary, or colon. Patients were excluded from the study if any of the following conditions were met: patient age less than 18 years, multiple primary tumor types, non-chemotherapeutic agent(s) administered as monotherapy, inpatient administration of chemotherapy, or unavailable chart.

Data collection

Eighty-four records meeting the above inclusion criteria were identified. These records were reviewed and data was extracted using a standardized data collection form that included demographic information, primary tumor type, chemotherapy regimen, staging at diagnosis, presence of disease progression, and mortality status. In determining the RDI, the following chemotherapy regimen data was collected: chemotherapeutic agents used, dosages administered, dates of administration, treatment intent (adjuvant vs. metastatic), and granulocyte colony-stimulating factor (G-CSF) usage per cycle.

After patient eligibility was determined and data collection was completed, the chemotherapy regimen data was entered into the NearSpace® RDI Calculator software program (14). For each chemotherapeutic agent, the software program calculated the RDI based on the total milligram dose of drug administered, the patient's body surface area (BSA) or target area under the curve (AUC), and the time course of treatment. The program expressed the RDI for each chemotherapy agent as the percentage of the dose intensity delivered relative to the reference standard dose intensity for that agent. For patients with multiple chemotherapy agents in their regimen, the RDI was determined separately for each agent and then the average RDI was calculated for the entire regimen.

Statistical analysis

All data was analyzed utilizing descriptive statistics. Summary statistics were calculated to convey the central tendency of RDI. These summary statistics were expressed as the sample mean.

Ethics

This study was conducted in accordance with the protections of human subjects as specified by our Institutional Research Review Committee.

Results

In 2007, We identified 84 patients who met the initial inclusion criteria. Nineteen patients were excluded: 5 patients received non-chemotherapeutic agent(s), 4 patients had inpatient administration of chemother-

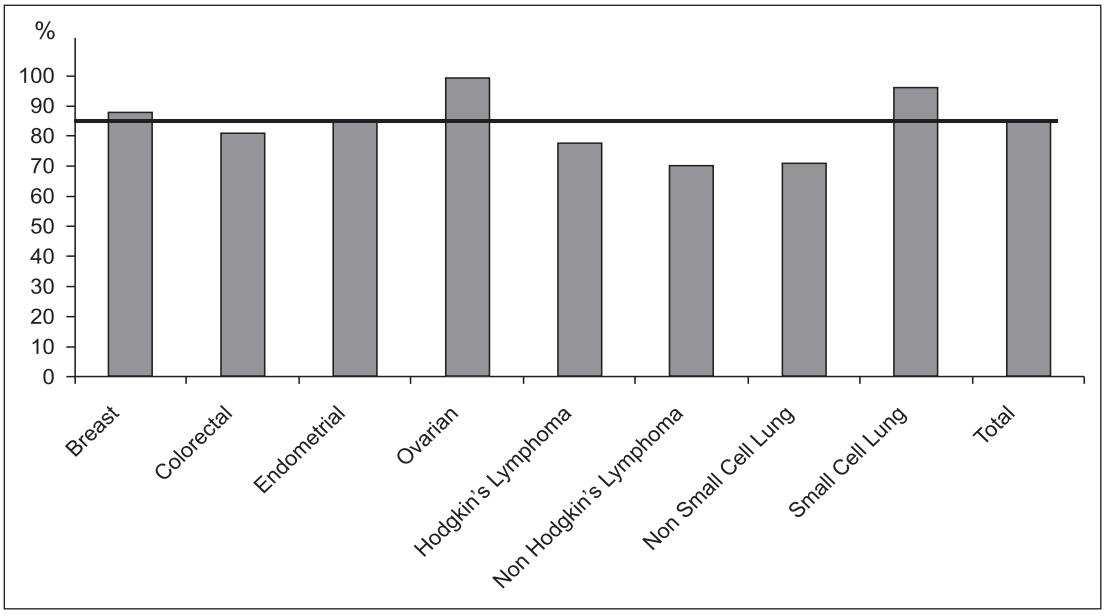

Figure 1 Average relative dose intensity by diagnosis. Black line denotes threshold RDI ≥ 85%

apy, 1 patient had more than one malignancy, and 9 charts were unavailable. Sixty-five patients were included in the final analysis. The overall RDI was determined to be 83%. The average RDI for patients receiving adjuvant chemotherapy (n=51) was 85% and for patients receiving chemotherapy for metastatic disease (n=14) the average RDI was 76%. The proportion of regimens that met or exceeded the 85% threshold RDI was 54%.

The average RDI was further analyzed by cancer diagnosis, disease progression, mortality status, and G-CSF use. RDI by cancer diagnosis is shown in Figure 1. The average RDI for patients diagnosed with breast, ovarian, and small cell lung cancer reached the desired goal of ≥ 85%, while the remaining cancer types did not.

Disease progression was documented in 22 patients. For these patients, the average RDI was 76%. Where disease progression was not documented (n=43), the average RDI was 86%. Analysis by mortality status revealed that the average RDI for expired patients was 73% (n=17), while patients who were alive averaged an RDI just above the desired range (86%, n=48). Use of G-CSF was documented in 69% (n=45) of patients; for 71% of cases, growth factors were administered as primary prophylaxis and for 28%, as secondary prophylaxis. The average RDI for patients who received G-CSF as supportive care during their chemotherapy was 82%.

Discussion

The overall RDI at our institution was slightly below the desired level of 85%; however, patients with potentially curable malignancies who received adjuvant chemotherapy just reached the threshold RDI. The results of this study provide valuable benchmarking data, allowing our institution to compare our practice patterns with that of other practices. In a nationwide survey by Lyman et al, 1,243 community oncology practices provided data for 20,799 patients with early-stage breast cancer (6). For patients receiving adjuvant chemotherapy, 55.5% received RDI < 85%. Another nationwide survey by

Lyman et al, focusing on 4,522 patients with aggressive non-Hodgkin's lymphoma, reported an RDI < 85% for 48 to 53% of patients receiving treatment at 567 oncology practices (7). Overall, our finding that 46% of our patients received RDI < 85% is consistent with results from these published studies. It is important to note that patients who experienced disease progression, or who expired, received chemotherapy at an RDI well below the threshold level. However, long term follow up (greater than one year) was not carried out in this analysis. More prospective studies are necessary to properly determine the impact of RDI on disease progression and survival, especially in the adjuvant setting, despite previous reports that reductions in chemotherapy dose intensity may compromise disease control and survival in patients with curable malignancies. Data shows increased survival for patients receiving greater than or equal to 85% RDI and conversely, mortality curves similar to untreated populations when this threshold RDI was not administered (12, 13). The use of referenced chemotherapy dose and timing are also important in order to achieve outcomes comparable to those achieved in clinical trials for that chemotherapy regimen (2).

Several limitations of this study should be considered. The RDI calculations included chemotherapeutic agents only. Targeted therapies, such as epidermal growth factor receptor inhibitors or vascular endothelial growth factor inhibitors, were not included in RDI calculations. To our knowledge, it has not been determined if these therapies confer a dose related impact on progression free survival or overall survival. Another factor to consider is that several patients expired prior to the completion of their planned treatment regimen (n=5). This group of patients had a low average RDI (40%) that negatively skewed the results of this study. Chart availability also limited the number of patients analyzed in this study. The majority of unavailable charts were cases in which patients were deceased.

The findings here indicate a need for quality improvement through the implementation of strategies for increasing the overall RDI administered to our patients. In order to improve the RDI administered at our institution, it is important to understand the barriers to delivery of full-dose, on-schedule chemotherapy. Reductions in dose and delays in therapy both hinder the delivery of full-dose, on-schedule chemotherapy and in turn, reduce the RDI achieved (15). Dose delays and reductions can be either treatment related or non-treatment related. Common treatment related causes include: empiric dose reductions, reductions due to myelosuppression (ie. neutropenia), and other drug specific toxicities (15, 16). Non-treatment related causes include: lack of patient and/or provider awareness of the importance of full-dose, on-schedule chemotherapy and visit cancellations (15). Patient-initiated visit cancellations often occur due to personal or family illness, social events, lack of transportation, or miscommunication. Typically, missed appointments are rescheduled for the following week, resulting in week-long chemotherapy delays. When chemotherapy dose delays and reductions are employed together to avoid excessive toxicity or to improve tolerability, negative outcomes of RDI reductions are magnified (16). Dose delays and reductions often result in only nominal decreases in toxicity, but considerable reductions in the capacity to attain a complete remission in patients with drug-responsive tumors (2, 17).

Many different strategies may be utilized in clinical practice to improve RDI. Practice-related interventions may include dose-dense or dense-intense treatment strategies, patient and family education, staff education, prospectively calculating and documenting regimen RDI, risk assessment for

febrile neutropenia, optimizing the use of supportive care agents (G-CSF), and utilization of a strict cancellation protocol (3, 15). Based on the findings from this study, our institution has undertaken a major quality improvement initiative to improve the RDI of systemic chemotherapy. Our main focus has been prevention of chemotherapy dose reductions and delays, specifically the evaluation of G-CSF use and visit cancellations. The next evaluation component is being conducted in four different phases: 1) a one-month pilot study to determine G-CSF utilization and systemic chemotherapy appointment cancellation frequency; 2) cancellation policy development, febrile neutropenia risk assessment tool implementation, and staff education; 3) cancellation policy and risk assessment tool implementation; and 4) post-intervention prospective determination of the RDI at our institution. This follow-up study will not only allow our institution to identify potential areas for improvement but to also to implement strategies that will enhance patient outcomes.

Conclusion

Overall the average RDI at our institution was 83%, slightly below the goal of ≥ 85%. Although patients with potentially curable malignancies receiving adjuvant chemotherapy reached the threshold of 85%, areas for quality improvement exist at our institution. Potential strategies for improvement include: staff education, optimized use of G-CSF, and a strict cancellation policy. Other institutions are encouraged to examine the RDI of systemic chemotherapy at their sites and to develop strategies with regard to improving and/or maintaining optimal RDI.

Conflict of interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organisation.

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