Automated chemotherapy compounding: Process optimization for the preparation of admixture containing high-dose of cyclophosphamide

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Keywords
Cyclophosphamide, automated chemotherapy compounding, hematologic malignancies, peripheral blood stem cell mobilization, autologous stem cell transplantation

Date received: 1 June 2022; revised: 13 September 2022; accepted: 15 September 2022

Cyclophosphamide (CTX) is one of the most used drugs in the treatment of solid and hematologic malignancies. Autologous stem cell transplantation (ASCT) is nowadays the standard of care as an upfront approach for patients suffering from multiple myeloma and non-Hodgkin lymphoma.

Under this light, granulocyte-colony stimulating factor (G-CSF) with or without CTX is a common regimen for peripheral blood stem cell (PBSC) mobilization.¹

Successful stem cell mobilization and adequate collection of PBSCs are essential for patients undergoing ASCT.

Different mobilization protocols have been used: plerixafor, a CXCR4 inhibitor, is commercially available and its use is a standard of care in clinical practice.² Even if the efficacy of plerixafor has been previously proven, particularly in patients who failed mobilization with G-CSF, the cost of single administration cannot be ignored.³ At the same time, CTX and G-CSF protocol, which has been efficiently applied for more than 25 years, is less expensive but often associated with serious treatment-related adverse events, like neutropenia, neutropenic fever, and hematuria.⁴,⁵

It is well known that antineoplastic drugs are recognized as potent hazardous drugs due to their inherent carcinogenic, mutagenic, and nephrotoxic properties. The occupational exposure of healthcare workers to these drugs was highlighted several decades ago and represents still a matter of concern.⁶ Many studies have reported CTX as a frequent contaminant drug on the surfaces of pharmacy compounding areas.⁷

Therefore, in order to minimize the risk of occupational exposure of healthcare workers, containment measures must be implemented, especially when high doses of cytotoxic drugs are handled or powdered drugs reconstituted. Of note, high-dose CTX combined with G-CSF represents currently the standard of care for PBSC mobilization at our institution.

The adoption of ready-to-use admixture of CTX represents an option aimed at speeding up the preparation process and lowering the risk of occupational exposure thanks to the omission of the reconstitution procedure with the consequent release of aerosols or vapors. Ready-to-use admixtures of cytotoxic drugs are commercially available in our country: CTX is produced as a standard concentration of 20 mg/ml in a single 250 ml bag containing 5000 mg CTX. The adoption of CTX ready-to-use admixture could be expensive, but convenient in terms of preparation time and workers safety. However, the implementation of an alternative procedure is possible.

In October 2020, the robot APOTECAchemo (Lecchi, Italy) for totally automated cytotoxic drugs compounding has been implemented in the pharmacy-based cytotoxic drugs preparation unit of our institution. Automated compounding of cytotoxic drugs is performed by a robotic system with little or no human intervention. APOTECAchemo is designed to reduce medication errors and the risk of exposure to carcinogenic substances while ensuring proven rather than assumed dosage accuracy, sterility, full traceability, documentation, and lower risk of needle stick injuries and physical complaints.⁸

Barcode

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recognition, label identification of the source products, and gravimetric verification are used for in-process controls and process documentation. The robot can handle different types and sizes of final containers (syringes, infusion bags, elastomeric pumps), prepare both patient-specific and standard doses, and process liquid and reconstitute powdered drugs.

In the 14 months of operation following the implementation (January 2021–February 2022), 18,351 preparations were compounded with the robot. The number of active ingredients processed is 40, including conventional anticancer drugs and monoclonal antibodies. The average weekly production amounts to 353 preparations. Overall, 18,167 (99.0%) preparations presented a mean compounding error (dosage accuracy) lower than ±5%. Under this light, different questions need appropriate answers:

- Could the implementation of totally automated compounding of ready-to-use cytotoxic drugs substitute (albeit partially) the adoption of commercial ready-to-use admixtures?
- Could the in-advance reconstitution of the powdered drug, such as CTX, represent a safe and effective way to optimize the compounding process and achieve cost savings?
- Could this practice be justified by the physicochemical and microbiological stability of drugs?

With this in mind, we performed a preliminary analysis of the current practice at our institution with the aim to try to reel off the pros and cons of automated manipulation of CTX, if possible.

In 2021–2022, 27 PBSC mobilization with CTX/G-CSF protocols were conducted, and the mean CTX dose amounted to 7360 mg, equivalent to eight 1000 mg CTX vials per treatment.

The standard procedure for the reconstitution of two 1000 mg CTX vials with APOTECAchemo on average takes 20 min. The process time was calculated from the loading of the vials into the rotating carousel until the end of the reconstitution process. The shaking time set to thoroughly dissolve one powdered drug vial was 6 min.

During this process, the robot records all the details regarding the batch and expiration date of drugs and solvents used. Finally, a detailed report is automatically generated by the system including all the crucial information, such as % discrepancy between the prepared and prescribed drug quantity, expiration date after manipulation, storage conditions, and a unique barcode, useful for subsequent recognition of single vials with all related data.

In our routine practice, the use of PBSC mobilization was previously established, in advance for several days or weeks, thereby allowing in-advance preparations. Analyzing the daily workflow of our compounding unit, we noticed a reduction of activity in APOTECAchemo in the morning between 9:30 and 10:30 a.m. and in the afternoon between 2:30 and 4:00 p.m. These time windows have been potentially identified as optimal for automated reconstitution of CTX when needed, thereby improving the productivity of the robot and the working efficiency of the personnel involved in the compounding activities. This approach implies also important advantages in terms of cost saving. Indeed, 1 mg of commercially available ready-to-use CTX costs 300% more than 1 mg of the powdered drug. In addition to costs and resources optimization, maintenance of high quality and safety standards is ensured by full traceability of all the procedures.

To assign an expiration date to ready-to-use and pre-reconstituted powdered drug vials, the pharmacists according to data previously published established the physicochemical stability. The extension of the beyond-use date is under the pharmacist’s responsibility. As regard microbiological stability, a validation process and subsequent monitoring plan must be implemented as per institutional guideline according to requirements set by Pharmacopeia and European GMP. A study conducted by Geersing et al. reported that robotic compounding of cytotoxic drugs with APOTECChemo met the microbiological requirements of the European GMP.

Our assessment revealed potential advantages when the production of ready-to-use pre-reconstituted CTX vials was performed with APOTECChemo: lower exposure of healthcare workers, cost saving, maintenance of high-quality standards, reduced environmental contamination of the compounding facilities, and improved working efficiency. Overall, according to our experience, automation impacts the workflow of centralized compounding of cytotoxic drugs and the entire production system should be analyzed and adjusted consequently. Robotic compounding may have a crucial role in the preparation of chemotherapy agents, ordered in advance and with long expiry and low cost, such as CTX.

In conclusion, the automation of chemotherapy compounding has the potential to offer both clinical and economic benefits in the hospital pharmacy. Further evaluations are needed in order to establish optimal implementation of automation in chemotherapy compounding. We accepted the “call to action” by Batson et al.: pharmacists must be encouraged to publish data following the implementation of chemotherapy compounding technologies, albeit preliminary, which would drive decisions for evidence-based recommendations on the benefits of chemotherapy compounding technologies and their real utility.

**Author contributions**

All authors contributed equally in design of the study, collection of data, analysis, interpretation and drafting the manuscript. All authors reviewed and approved the final version of the manuscript.
Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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