Review Article

Sequencing of antineoplastic drug administration: contributions to evidence-based oncology nursing practice

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ABSTRACT

The objective of this study was to find scientific evidence of drug interactions between antineoplastic drugs that result from the administration sequence and then describe the best sequence and discuss its applicability to nursing care systematization (NCS). An integrative review of the literature was carried out in 2018 in the MEDLINE, LILACS, CINAHL, and BVS databases, with the terms *neoplasms, drug Therapy, drug Interactions*, *chemotherapy*, and *sequence of administration*. Fifty-seven studies were analyzed, which, as a set, studied 40 combinations of antineoplastic drugs and found pharmacokinetic and pharmacodynamic interactions resulting from the sequence of administration, which supported the construction of a chart that indicates the best sequence for each of those combinations. Along with the chart, a flowchart was also made to support NCS in the context of evidence-based oncology nursing practice. Selecting the sequences of antineoplastic drug administration is a new conceptual strategy designed for nurses who carry out multidrug therapy.

Descriptors: Drug Therapy, Combination; Drug Interactions; Neoplasms; Oncology Nursing.

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INTRODUCTION

Antineoplastic drugs are a major class of medicines used to fight cancer. Because of their complex administration, it is recommended that only qualified nurses[1] administer them, since their evidence-based practice can properly handle the therapeutic and toxic effects of the treatment by means of a proper sequence of administration.

Since they are subject to the same pharmacokinetic and pharmacodynamic principles as any drug, antineoplastic agents have the same potential with regard to drug interactions. Considering that chemotherapy schemes generally use two or more drugs, the chances of interactions taking place get worse the higher the number of prescribed drugs is. Many of these interactions have significant clinical importance, since they can be minimally detrimental or sometimes even desirable. On the other hand, other interactions can have severe adverse effects, accounting for the death of about 4% of cancer patients.[2-3]

For a long time, antineoplastic drugs with different actions have been combined with the purpose of overcoming drug resistance and increasing the dose and density of cytostatics. However, studies on the mechanisms through which cells enter and carry on the division cycle have contributed to a better association of drugs in current chemotherapy protocols. The acknowledgment of several checkpoints responsible for regulating the cell cycle allowed for an improvement of the clinical efficiency of therapeutic treatments and made it evident that the sequence of drug administration can maximize therapeutic effects without increasing clinical toxicity. These effects can be explained by cell cycle disturbances provoked by chemotherapy or by pharmacodynamic interactions between combined agents.[4]

In that sense, and considering that most adverse drug interactions can be avoided with adequate planning of the infusion order, it is essential to study, assess, and acknowledge them so as to reduce mistakes, morbimortality, and costs related to iatrogenesis., A recent study on increasing cancer patient safety in chemotherapy showed the efficiency of multiprofessional interventions that protect patients, such as the implementation of a bar code prior to the administration of cytostatics, electronic prescriptions, pharmaceutical checks, the use of standardized drugs, and a manual of drug interactions to avoid mistakes in the administration sequence.[5]

Despite the consistency of published results that support the administration sequence of certain protocols, there is a lack of data that provide good levels of evidence for others, especially those that include more recent drugs that are not usually used in practice. In the analysis of synergy, antagonism, and therapeutic and toxic effects, the results remain controversial for many combinations of cytostatics, and clarification by means of scientific evidence is needed.

The Oncology Nurse Society (ONS), the body that defines safety rules for chemotherapy administration, still does not have specific guidelines for the administration of antineoplastics, but it highlights the importance of creating institutional protocols and care standards that provide excellent care services.[6]

In view of the above, and to support clinical decision-making, the objective of this study was to find scientific evidence on interactions between antineoplastic drugs that result from the sequence of administration and then describe the best sequence and discuss its applicability to nursing care systematization (NCS).

METHOD

This is an integrative review of the literature carried out in six steps: (1) formulation of the study question; (2) definition of the procedures for searching for evidence; (3) data collection; (4) data analysis; (5) critical analysis and interpretation; and (6) summary and presentation of results.(7)

This review aimed at answering the following question: "What are the interactions between antineoplastic drugs resulting from administration sequence?" The inclusion criteria were primary studies that addressed antineoplastic drug interactions, resulting from administration sequence, that were approved for human use in Brazil by the National Health Surveillance Agency, and that were published in Portuguese, English, or Spanish. Publications without a clear and reproducible methodology were excluded, as were those found in more than one database and those that addressed the sequence of oncology protocols and not the sequence of drugs.

Between January 18 and February 28, 2018, the databases Medical Literature Analysis and Retrieval System Online (MEDLINE), via PubMed; the Health Virtual Library (BVS, per its acronym in Portuguese); the Cumulative Index of Nursing and Allied Health (CINAHL); and Latin American Caribbean Literature on Health Sciences (LILACS) were scanned, without a definite time frame. Other studies were included by means of cross-reference.

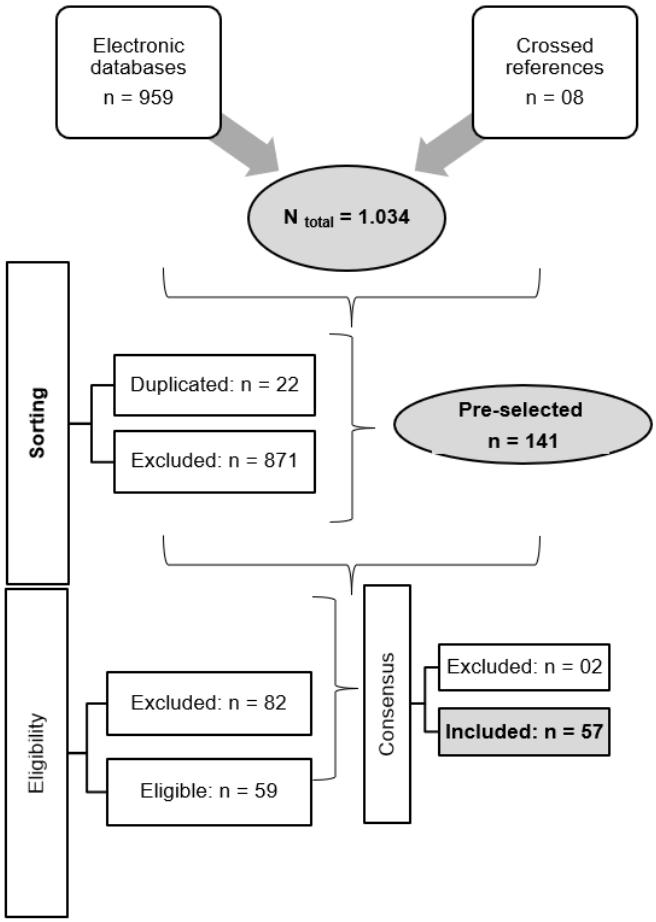
To define the method of search and identification of descriptors, a PIO strategy was adopted: (P) Population/problem = neoplasia; (I) Intervention = administration of antineoplastic drugs; and (O) Outcomes = synergistic interactions resulting from the administration sequence. The selected descriptors and MeSH were neoplasms, drug therapy, and drug interactions. The keywords chemotherapy and sequence of administration were also used. The terms were articulated by means of Boolean operators OR and AND.

The selection of publications was made in three steps. At the sorting stage, filters were applied to the databases in order to exclude unwanted studies, and afterward, duplicated studies. At the eligibility stage, inclusion and exclusion criteria were applied after reading titles and abstracts; at the inclusion stage, entire texts were read by two independent reviewers who agreed upon the inclusion or exclusion of the material selected at the previous stage, and the final sample was eventually determined. The included publications were then analyzed, summarized, and discussed in view of the proposed objectives.

RESULTS AND DISCUSSION

The searches found 1,034 publications, 57 (5.5%) of which made the final sample (Figure 1).

Figure 1: Flowchart of the selection process of scientific literature.



The 57 studies were published in English, in international journals, between 1973 and 2013, with the highest number of publications in 2001 (n = 6). Most of them were published in pharmaceutical and oncology journals, among which were the *Journal of Clinical Oncology* (24.6%) and *Cancer Chemotherapy and Pharmacology* (14%). There was no dissemination of the topic in nursing journals, which suggests the need to associate pharmacokinetic and pharmacodynamic studies with drug administration practices, since avoiding undesirable interactions by means of an adequate sequence is a technical and legal competence of nurses.

As for the method used to identify interactions, 27 studies (47.4%) carried out in vitro trials, which are defined as poor evidence to support specific recommendations. The significant number of interactions documented in these studies, which show synergy and antagonism resulting from the administration sequence, points to the need for investigation of the effects of a sequencing in clearly outlined clinical trials.

The pharmacokinetic and pharmacodynamic reasons for sequencing antineoplastic drugs and the clinical impacts observed are presented in Chart 1, which can be made available for use in treatment centers as an instrument to support decision-making.

Chart 1: Administration sequence recommended for antineoplastic combinations with the respective pharmacokinetic, pharmacodynamic, and clinical reasons, and levels of evidence (LoE) of studies. Brazil, 2018.

Administration sequence	Pharmacokinetic, pharmacodynamic, and clinical reasons for sequencing	LoE*
MTA-DTX	Higher antitumor effectiveness[8]	IV
PTX-GEM	Synergistic interactions, cell growth inhibition, and higher apoptosis rate in breast cancer cells. PTX increases significantly the dFdCTP cell content (GEM active form), enhancing its action.[9]	IV
5FU-MTX	Synergistic tumor activity; 5-FU allows a higher number of cells to enter stage S. In vivo, 5-FU administered before MTX reduces toxicity in the bone marrow and increases cytotoxic selection for neoplastic cells, possibly due to reduced folate preservation.[10] An overall survival increase in a randomized clinical trial favors the sequence 5-FU-MTX,[11] and the reverse sequence is not recommended.[12]	II
GEM-OXA	In vitro synergy and a higher apoptosis rate in the sequence GEM-OXA, with antagonism in the reverse sequence. The flow cytometry reveals that GEM interrupts the cell cycle at stage G0/G1, and OXA at stage G2/M. OXA destroys the cells that are recovering from the damage caused by GEM at stages G1 and S, leading to apoptosis at stages G2 and M. If OXA is administered first, it blocks cells at stage G2/M, reducing GEM action at stage S of the cycle in which it is more active.[13]	IV
OXA-5-FU	Increase in the apoptosis rate[14]	IV
CBDCA-DTX	Without pharmacokinetic interactions; mechanism of the toxic effect in reverse sequence not totally clear; fewer side effects and better therapeutic response[15]	II
GEM-DTX	Synergy in the sequence[16]; GEM pharmacokinetics are significantly changed by DTX administration, which may interfere in GEM dissemination and delay clearance elimination after this stage. Sequencing did not have a significant clinical impact.[17]	III
DTX-NVB	Polysorbate 80 found in DTX interferes with glycoprotein P, and it is responsible for controlling NVB blood levels and reducing myelotoxicity of the sequence DTX-NVB[18]; Cmax and AUC of NVB are significantly higher in the reverse sequence, increasing the toxic effects[18-19]; Cmax, AUC, and DTX clearance did not vary in either sequences[19]; lower potential for neutropenia[18]; lower hematological toxicity.[19]	III
GEM-CBDCA	Greater synergy[20]	IV
OXA-CPT-11	Synergy[21]	IV
EPI-PTX	The AUC for EPI was greater in the sequence PTX-EPI. An inverse linear correlation was also observed between the AUC for EPI and neutrophil recovery. No difference was detected in PTX pharmacokinetics. No significant difference in nonhematological toxicity. Lower platelet nadir and neutrophiles, with slower neutrophile recovery in the sequence PTX-EPI. Higher myelotoxicity.[22]	III
VCR-CDDP	VCR-CDDP is higher than the reverse sequence and simultaneous administration of the drugs. Higher cytotoxicity. The benefits of the sequence can result in damage to the microtubules, induced by VCR and modulated by CDDP. Antagonism in the cytotoxic effect of VCR when CDDP is administered before.[23] When cells are treated with CDDP, the cell cycle at stage S can be delayed and/or cells can be blocked in a reversible way at G2,[24] resulting in inhibitors of the spindle apparatus missing the cell cycle stage that are more sensitive to their action.[23]	IV
PTX-CDDP	In vitro antagonism in sequence CDDP-PXT. This antagonism was also seen when both drugs were administered simultaneously. By contrast, the sequence PXT-CDDP resulted in additive or synergistic interactions.[25-26] The antagonism observed can be related to the effects in the cell cycle that were induced by CDDP or to changes in PXT binding sites. In vitro data suggest that clinical protocols that use the sequence CDDP-PXT can have reduced therapeutic efficiency, and therefore they must be avoided.[26] Synergistic interactions between drugs do not explain the clinical efficiency of the combination.[27] Clinical data show a reduced total body clearance of PXT of 25% in patients who were given CDDP before. There is severe neutropenia in the reverse sequence.[25,28] The combination PXT-CDDP is considered to be an active regimen but also neurotoxic. Longer administration of PXT results in greater neutropenia than shorter ones.[28]	III

Administration sequence	Pharmacokinetic, pharmacodynamic, and clinical reasons for sequencing	LoE*
CTX-PTX	The administration of CTX delays the cell cycle from stage G2 to M, reducing the cytotoxicity of normal cells mediated by PXT, and consequently a PXT-induced myelosuppression that occurs regardless of the PXT administration lasting 3 or 24 hours.[29] Neutropenia and thrombocytopenia were greater in the reverse sequence. Higher hospitalization rate for febrile neutropenia.[30]	III
PTX-IFO	Antagonistic effect in the reverse sequence. Additive/synergistic effect if administered 24 hours before or simultaneously.[31]	IV
PTX-VP-16	Time-dependent antagonistic effect in the reverse sequence. Pretreatment with VP-16 reduces significantly the PXT activity for up to 24 hours. However, the decrease in PXT cytotoxicity is not observed when the drugs are administered with a 48- or 72-hour interval.[31]	V
ADM-PTX	The pharmacokinetic interactions between PXT and ADM are responsible for the increase of ADM blood concentrations and of its metabolites. The interference in the sequence-dependent pharmacokinetic profile is due to a change in the hepatic clearance of ADM induced by the PXT pretreatment. There is a possible competition for the biliary excretion between taxanes and anthracyclines mediated by P-gp.[32] In the sequence PXT-ADM, ADM concentrations at the end of administration (Cmax) were 70% higher compared to the reverse sequence. Its clearance was 32% lower. The pharmacokinetic changes were responsible for the increase in mucositis and neutropenia.[33] PXT interfering with ADM pharmacokinetics results in a greater systemic exposure of doxorubicin and its metabolite, doxorubicinol. This interference can explain the higher incidence of cardiotoxicity, which is observed when two drugs are administered within a short period of time.[34]	III
CPT-11-TDX	Synergistic cytotoxicity. The reverse sequence produces fewer additive and enhancing effects. TDX inhibits TS directly and selectively. TDX polyglutamylation allows for a longer intracellular reabsorption and improves affinity for TS. Pretreatment with CPT-11 can increase cell proportion at stage S, which is more sensitive to TDX action. The reverse sequence results in a lower TS inhibition than the DNA synthesis; it reduces the creation of cleavage complexes in broken DNA chains, and therefore it reduces the efficiency of the combination.[35]	IV
5-FU-HER-2	Synergy in the sequence. HER-2 reduces the proportion of cells at stage S, hampering the antitumor effects of 5-FU, and inhibits the transduction of HER2–PI3K–AKT induced by trastuzumab.[36]	IV
MTA-GEM	Synergy[37]	IV
ARA-C - LDP-341	Proteasome inhibition is marked in cells pretreated with Ara-C. The increase in proapoptotic molecules in the sequence favors apoptosis. In the reverse sequence, LDP-341 interrupts cells at stage G2 and M, reducing DNA replication. This mechanism reduces the cells at the cell cycle stage that is more sensitive to ARA-C.[38] The inhibition of proteasomes before exposure to Ara-C can reduce the incorporation of nucleoside analogues to the DNA, a mechanism by which Ara-C acts as a false metabolite. The LDP-341-induced accumulation of Mcl-1 can also interfere in ARA-C effectiveness.[39]	IV
LDP-341-DHAQ	Antagonism of the reverse sequence. Inhibitors of proteasomes stabilize topoisomerase 2-alpha and revert neoplastic cells resistance to topoisomerase inhibitors.[38]	IV
GEM-LDP-341	Greater induction of apoptosis and inhibition of tumor cell growth[40]	IV
FAMP-ARA-C	FAMP provides a biochemical modulation of ARA-C. F-ARA-ATP increases Ara-C anabolism, whereas in the reverse sequence Ara-C changes FAMP pharmacokinetic negatively. The terminal half-life of F-ARA-A in blood and half-life of intracellular F-ARA-ATP (FAMP metabolite) were reduced after the administration of ARA-C. The terminal half-life of F-ARA-A was reduced in proportion to the blood levels of ARA-C. A faster clearance of F-ARA-A from the blood after treatment with ARA-C shows a shorter retention of the drug in tissues.[41] The administration of FAMP before ARA-C increases the metabolism of ARA-CTP in leukemic lymphocytes.[42] Greater clinical benefits were observed in recurrent leukemia.[41]	III
CTX-CDDP	Synergy in the sequence, showing marked inhibition of clonogenic growth of tumor cells[43]	IV
BLEO-PTX	Synergy, whereas in the reverse sequence there is lower cytotoxicity. BLEO can block the progress of cell cycle at stage G2/M more sensitive to PXT.[44]	IV
TPT-DTX	The reverse sequence causes a decrease of 50% in TXT clearance; lower potential for neutropenia.[45]	II

Administration sequence	Pharmacokinetic, pharmacodynamic, and clinical reasons for sequencing	LoE*
CPT-11-5-FU	Synergy, with clear antiproliferative effects that depend on this sequence.[46-48] When CPT-11 precedes the administration of 5-FU, there is a decrease in the AUC of SN-38 metabolite. The tolerated maximum dose of CPT-11 is 450mg/m^2 when its administration precedes that of 5-FU and 300 mg/m^2 when administered subsequently. Dose-limiting toxicity was better observed when CPT-11 followed the use of 5-FU. The pharmacokinetic analysis reveals that the administration sequence has a significant effect on the SN-38 AUC, which is 40.1% lower when CPT-11 precedes the use of 5-FU.[49] There is an increase of stage S cells (sensitive to 5-FU) provoked by SN-38.[47]	II
GEM-NVB	NVB can have an influence on the deamination of GEM to dFdU (its metabolite) through the deoxycytidine deaminase found in the liver. GEM can have an influence on the metabolism and liver clearance of NVB in this sequence, reducing its AUC_{tot} and toxic effects.[50]	II
TPT-CDDP	The sequence CDDP-TPT induced significantly higher neutropenia and thrombocytopenia than the reverse sequence. This fact can be explained by the lower TPT clearance and the increase of its blood exposure caused by CDDP-induced subclinical renal toxicity. The in vitro method failed to explain pharmacodynamic mechanisms.[51]	III
CDDP-CETUX **CBDCA-CETUX** **OXA-CETUX** **DTX-CETUX**	Synergy. Higher cytotoxic effect in the presented sequences. The exposure to inhibitors of epidermal growth factors has an antagonistic effect when they are administered before chemotherapy, showing negative kinetic interactions in the cell cycle.[52]	IV
TPT-DTX	Neutropenia decrease. The reverse sequence leads to a 50% decrease of docetaxel clearance.[45]	III
GEM-CDDP	The sequence GEM-CDDP has a higher apoptosis rate, with more cells blocked at stages G1 and G2 of the cell cycle. Gemcitabine increases intracellular absorption of CDDP and subsequent DNA platination. CDDP inhibits the activity of ribonucleotide reductase and it can reduce GEM metabolism.[53] The inhibition of DNA synthesis and blocking of cells at stage S can be crucial to the sequence-depending interaction.[54] It was observed in vivo that treatment with GEM followed by CDDP was 54% more efficient.	III
PTX-OXA	Greater synergistic activity. The sequence PTX-OXA in vitro led to a 75% apoptosis. When cells recover from the PXT-induced blockage at stage M, progressing to stage S, they are destroyed by the subsequent administration of OXA. There is antagonism in the reverse sequence, with only 39% of apoptosis rate. Previously administered OXA leads to cell buildup at G1/S, a stage at which they are not sensitive to PXT.[14]	IV
TPT-CBDCA	Lower myelotoxicity, but TPT and CBDCA clearance do not depend on administration sequence. Level-4 thrombocytopenia was more severe in the arm in which the sequence C-T was administered. This combination has important implications for nursing: level-4 nausea and vomiting, febrile neutropenia and thrombocytopenia are expected effects. They have dose-limiting toxicity.[56]	III

* Considering the study with higher levels of evidence[57]

MTA: Pemetrexed, DTX: Docetaxel, PTX: Paclitaxel, GEM: Gemcitabine, 5-FU: Fluorouracil, MTX: Methotrexate, OXA: Oxaliplatin, CBDCA: Carboplatin, NVB: Vinorelbine, CPT-11: Irinotecan, EPI: Epirubicin, VCR: Vincristine, CDDP: Cisplatin, CTX: Cyclophosphamide, IFO: Ifosfamide, VP-16: Etoposide, TDX: Raltitrexed, HER-2: Trastuzumab, ARA-C: Cytarabine, LDP-341: Bortezomib, DHAQ: Mitoxantrone, FAMP: Fludarabine, BLEO: Bleomycin, CETUX: Cetuximab. AUC: Area under the curve, TPT: Topotecan, TS: Thymidylate synthetase.

For six combinations of antineoplastic drugs, some studies did not find differences in pharmacokinetic profiles that depended on administration order (Chart 2).

Chart 2: Combinations of antineoplastic drugs without pharmacokinetic interactions that depend on administration order, as shown by some studies. Brazil, 2018

Sequence	Results
OXA-CPT11[58]	No pharmacokinetic interactions were detected between these agents. The main toxicities were neutropenia and late diarrhea, regardless of administration order.
GEM-OXA[59]	The sequences GEM-OXA and OXA-GEM showed a similar pharmacokinetic pattern, with no sequence-depending interaction.
PTX-CBDCA[60-62]	Carboplatin pharmacokinetics were not altered by PXT pretreatment with the standard dose. Pharmacokinetic interaction is not responsible for the lower toxicity of the combination. Neutropenia is the main effect, anemia is frequent, and thrombocytopenia has a lower incidence.
BEVA-CPT-11[63]	BEVA does not affect CPT-11 pharmacokinetics. A variety of pharmacogenetic relationships can have an influence on CPT-11 pharmacokinetics and its toxicity.
CDDP-CPT-11[64]	No pharmacokinetic changes are the result of administration order. This combination provides a practical and well-tolerated regimen, with potential synergy enhancement between agents.
ADM-PTX[65]	The administration order does not affect pharmacokinetics and toxicity. High complete response rates and congestive heart failure are the expression of therapeutic and toxic effects of this combination.

OXA: Oxaliplatin, CPT11: Irinotecan, GEM: Gemcitabine, PTX: Paclitaxel, CBDCA: Carboplatin, BEVA: Bevacizumab, CDDP: Cisplatin, ADM: Doxorubicin

For the sequences bevacizumab-irinotecan (BEVA-CPT-11),[63] cisplatin-irinotecan (CDDP-CPT-11),[64] oxaliplatin-irinotecan (OXA-CPT-11),[58] and paclitaxel-carboplatin (PXT-CBDCA),[60-62] there were no clinical effects in terms of toxicity or therapeutic benefits. As for the sequence PXT-CBDCA, although this study did not find scientific evidence to support it, the literature strongly recommends this order. The justifications are based on the risk of neutropenia caused by platin analogues when they precede taxanes in the sequence, and on the risk of lesions secondary to extravasation of vesicant agents, such as PXT.[66]

Controversial results[32-34,65] for the sequence doxorubicin-paclitaxel (ADM-PXT) (Charts 1 and 2) are partly due to the small sample size and to the genetic variability observed among individuals. Genetic polymorphisms are responsible for the diversity of the load of inducing and metabolizing enzymes and influx carriers, resulting in different responses and degrees of interaction between drugs. It has been suggested that genetic factors can contribute to 20–95% of the variability of the therapeutic and toxic efficiency of ADM. Therefore, the understanding of ADM metabolic pathways has demonstrated pharmacogenetic, pharmacokinetic, and pharmacodynamic correlations, favoring therapy individualization.[67-68] Likewise, some studies have shown that longer ADM infusion times may not only result in changes of pharmacokinetic standards but also in cardiotoxicity, which conflicts with the results of the analyzed studies. In this context, pharmacokinetic interactions with the combination were best described in studies with PXT administered for 24 hours instead of 3 hours.[69] The reviewed publications that advocated for the sequence ADM-PXT were clearly better than those that suggested a lack of interaction for the sequence. Given the importance and consequences of a rise in plasma concentrations of doxorubicin,[70-72] this article recommends ADM-PXT.

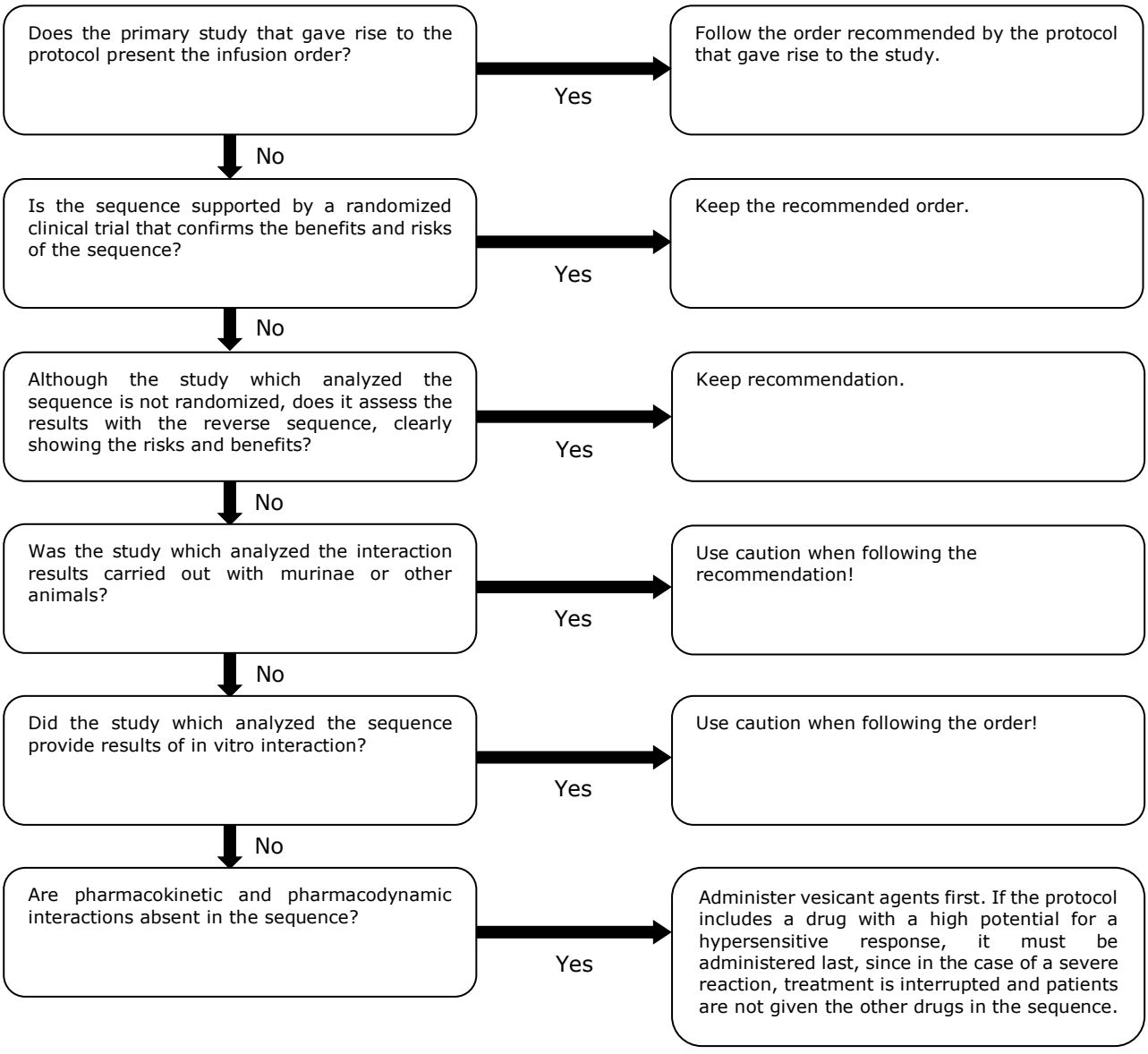
For the sequence gemcitabine-oxaliplatin (GEM-OXA), favorable *in vitro* results[13] (Chart 1) did not bring better clinical *in vivo* benefits[59] (Chart 2), reinforcing the need for caution in its interpretation and practical use.

DISCUSSION

Administering chemotherapy in the wrong order is considered a medication error, and it is the most common cause of error (50.5%) among nurses who work in outpatient chemotherapy centers.[73] This finding confirms the relevance of planning the infusion order on the basis of good levels of evidence to support decision-making, as recommended by evidence-based practice (EBP).

With the purpose of guiding the administration sequence performed by nurses, according to EBP, a flowchart is presented in Figure 2.

Figure 2: Flowchart of support to evidence-based practice of the administration sequence of antineoplastic drugs Brazil, 2018.



The antineoplastic sequence chart must be assessed along with the flowchart (Figure 2), since certain chemotherapy protocols already define the sequence and infusion length of drugs. They are enshrined because they come from stage III or IV multicenter studies and follow large populations of patients for a long time. Changes in their flow can hinder treatment effectiveness in terms of clinical benefits, overall survival, and safety.

To reduce the risks of a change in the sequence laid down in chemotherapy protocols, publications, such as oncology manuals and handbooks, containing a precise description of the regimen must be checked before the administration of drugs. If the order is not explicit for the concerned regimen, nurses are responsible for clarifying

the sequence as part of the nursing process. To do so, a nursing verification process is recommended through which expert nurses double-check the antineoplastic prescriptions, by checking the correct combination of drugs and calculating the body surface, the interval between cycles, the dose adequacy, the dilution standard, and the order and length of infusion.[74]

In the absence of pharmacokinetic and pharmacodynamic interactions, the literature recommends the administration of vesicant agents before nonvesicants in peripheral veins, as shown in the flowchart (Figure 2). This strategy reduces the risk of extravasation, since at the beginning of treatment, vessels are intact, that is, less affected by local reactions induced by other agents, such as erythema, pain, and pruritus.[75] When it comes to combinations with more than one vesicant agent, the risks and severity of lesions secondary to extravasation[76-77] justify the administration of vesicant agents, which bind to the DNA first, followed by those that do not bind, and finally, neutral chemotherapy drugs.

Although the best evidence available was analyzed so that Chart 1 could be made, it is worth mentioning that up to now, no systematic reviews and meta-analyses of antineoplastic drug infusion order were found, and such studies are considered to be of greater relevance for clinical decision-making, according to EBP.

With regard to evidence strength of in vitro studies, many of them analyzed the effect of the sequence of antineoplastic drugs through incubation of cell lines in drugs for 24 hours or longer. These results may not be consistent in supporting the practice of sequencing drugs administered on the same day in human beings. Despite strong evidence of effects on cell cycle induced by infusion order shown in these studies, the drug pharmacological action profile may vary significantly given the changes in pharmacokinetic patterns observed in vivo. Among these patterns, we can mention the plasma protein binding of the drug, and its distribution, metabolism, clearance, half-life, and action time in the body.

Studies with in vivo drug interactions that showed changes in pharmacokinetic patterns have major clinical relevance, since they determine with greater precision drug concentration in different body parts, the time it takes to get to the site, the duration and extent of the therapeutic/toxic effects, and time to clear.

Although in vitro studies can have limitations in supporting a given sequence in nurses' clinical practice, in the absence of in vivo interactions and when it comes to neutral agents (with no vesicant or irritant nature), they can provide a reasonable justification when determining infusion order. The findings of this type of study have important implications to the design of current chemotherapy protocols, since they provide important molecular information about the effects of drug interaction at a cellular level. Their careful review shows a large number of in vivo substrates for antineoplastic drugs, enzymatic inhibitors and inducers, responsible for metabolism and drug interactions[78].

In vitro methods are increasingly progressing with 3-D cell culture. In addition to the toxicity analysis related to drugs, they have a special importance in the assessment of drug administration strategies, with great potential in terms of specificity in target-driven therapy, drug interactions at cellular level, and the role of excipients in interactions. These new models offer the possibility to investigate advanced treatments, including genetic drugs and formulas with nanoparticles, and they promise consistent results in terms of sensitivity to drugs and toxic effects. Among the challenges to come, we can mention stronger in vitro-in vivo correlations to improve reliability and ensure safe use.[79]

In vitro studies therefore have value and cannot be ruled out for decision-making purposes. The lack of high-quality evidence for some antineoplastic drug sequences does not prevent EBP decision-making. In this situation, it is the best evidence available that is required, not the best evidence possible.[80]

The great variability and complexity of combinations of drugs and ongoing clinical regimens, in addition to a quick adoption of research protocols in conventional clinical treatments, have required a frequent retraining of doctors, nurses, and chemists in the search for better evidence.

Implications for Nursing Care Systematization

The most frequent negative effects found in sequence-dependent in vivo studies in this review were neutropenia[18,25,28,30,33,45,51,56] and thrombocytopenia,[51,56] which are closely related to nursing diagnosis of "risk of infection" and "risk of bleeding." Other toxic effects involved in the administration order were diarrhea,[49] hepatotoxicity,[50] nausea,[49] vomiting,[56] mucositis,[33] and cardiotoxicity,[34] which are also associated with nursing diagnosis, as provided for in the NANDA International classification system.[81]

In outpatient oncology services, care provided must focus on individuals' needs, with the help of nursing diagnoses as a standardized taxonomy. This tool provides support for decision-making and guides the choice of interventions that are more efficient in order to improve patients' response to antineoplastic treatments.[82]

A study that analyzed the nature and classification of nursing interventions in an adult chemotherapy outpatient facility found a predominance of actions aimed at nutritional advice, with no reports of nursing diagnoses of "risk of infection," nor interventions for its prevention/control and planning of drug administration order.[83] These findings are noteworthy, since this shortcoming increases patients' vulnerability to infectious complications, in addition to other effects resulting from errors in drug administration order. By means of effective planning of the infusion order, nurses can, in their practice, not only reduce the incidence and severity of these complications but also adjust doses and delays in treatment caused by severe and long-term myelosuppression.

Therefore, the nurse who administers antineoplastic chemotherapy is responsible for supervising and guiding care aimed at prevention of infections. Such interventions must be planned at the third stage of the nursing process,[84] considering the specific myelotoxic potential of the drugs, the time of nadir, and bone marrow recovery for the concerned protocol.[85] At the fourth stage of the nursing process, called the assistance implementation stage (nursing prescription),[84] some studies have prioritized interventions in elderly patients, patients with breast cancer and high-grade hematologic neoplasia, the control of neutrophil counting, prophylactic administration of hematopoietic growth factors,[85] and chemotherapy drug infusion, following an order that reduces the risks of febrile neutropenia. The last intervention is capable of providing the best therapeutic response, which comes from the biochemical and pharmacodynamic synergy between the agents involved in the sequence.

In view of the above, the planning of the infusion order must be done with the same thoroughness with which the device for vascular access is chosen and the catheter is inserted. Such actions are aimed at preventing skin lesions secondary to extravasation and reducing toxic effects resulting from an inadequate sequencing.

Recommendations to improve safety and reduce errors in chemotherapy administration include the implementation of standardized processes and strict compliance with policies and routine procedures, with the purpose of ensuring quality at all stages of the process.[6,74]

In this context, the antineoplastic drug sequence chart (Chart 1) can support the definition of standards for the infusion order and consequently improve the effectiveness of chemists and nurses by reducing waiting time in chemotherapy outpatient facilities with a high number of patients, avoid the preparation of drugs that will not be administered in the first place, and reduce the risks of errors resulting from wrong sequencing, drug skipping, protocol violation, and delays in treatment.

To improve patient safety, staff must be aware of the same information and carry out the same conduct regarding the clinical implications of the infusion order. The awareness of risks involved in this nursing action demonstrates the need for managers to highlight best practices when they create institutional protocols for cytostatic drug administration, which is part of NCS. In view of this new reality, it should be noted that an incorrect sequence of antineoplastic drugs is a risk to the physical integrity and survival of patients undergoing chemotherapy, and it requires the presence of highly skilled nursing professionals who are aware of evidence-based knowledge of the nursing process[85].

CONCLUSIONS

The administration of chemotherapy and its duration require a deep knowledge by nurses of its molecular, pharmacodynamic, and pharmacokinetic mechanisms. Selecting the sequences of combined antineoplastic drug administration, on the basis of these mechanisms, is a new conceptual strategy designed for nurses who carry out multidrug therapy.

The chart created in this study, which indicates the best sequences, is an instrument that can be easily consulted by nurses and chemists, and it can be made available for infusion services in order to contribute to the prevention or reduction of errors arising from an inappropriate infusion sequence. It aims to ensure lower toxicity and greater clinical benefits to patients as the result of a better synergistic interaction between drugs. In that sense, it is an important tool for NCS, which supports the management of risks for a safer care.

It is worth mentioning that a limitation of this study concerns the absence of studies with high levels of evidence capable of gathering the administration sequences for the main protocols used in clinical practice. Likewise, there are few studies that address NCS in the context of multidrug therapy. In view of the above, new studies that fill these knowledge gaps are necessary to support EBP and therefore ensure safer and more efficient care.

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