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Differences In The Occurrence Of Drug-Related Problems And The Duration Of The Assessment Of Pediatric Chemotherapy Prescriptions Before And After The Implementation Of The Electronic-Based Cytotoxic Drug Reconstitution Guidance System At Dr. Moewardi Hospital

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Abstract.

Introduction
Assessment of pediatric chemotherapy prescriptions is essential for preventing Drug-Related Problems (DRPs). A preliminary review showed that 57% of pediatric injectable chemotherapy patients were at risk of potential DRPs, contributing to prolonged assessment times. These issues indicate the need for systematic improvements to enhance medication safety and workflow efficiency. This study aimed to evaluate differences in DRP incidence and prescription assessment duration before and after implementing an electronic cytotoxic reconstitution guidance system.

Method
An experimental design was used to compare assessments before and after implementation of the electronic guidance system. A total of 60 pediatric chemotherapy prescriptions were analyzed, consisting of 30 assessed without the system (control) and 30 assessed after implementation (treatment). DRP occurrences were documented, and assessment duration was measured in minutes and seconds. Statistical analyses were performed to identify differences between groups, with significance set at $P < 0.05$.

Results
In the control group, 26 DRPs were identified, compared with 6 in the treatment group. Statistical analysis confirmed that the guidance system significantly reduced DRP incidence ($P < 0.05$). The mean assessment duration also decreased substantially from 7 minutes 2 seconds before implementation to 3 minutes 18 seconds afterward, and this reduction was statistically significant ($P < 0.05$).

Conclusion
The electronic cytotoxic reconstitution guidance system effectively enhances the safety and efficiency of pediatric chemotherapy prescription assessments. It significantly reduces DRP incidence and shortens assessment duration, demonstrating its value in improving workflow and supporting safer chemotherapy services.

Keywords: Assessment Duration; Cytotoxic Reconstitution; Drug-Related Problems; Electronic Guidance System; Pediatric Chemotherapy

Introduction

Prescription assessments are conducted to analyze drug-related problems; Each identified drug-related problems must be consulted with the prescriber doctor. Pharmacists must conduct prescription assessments as per administrative requirements, pharmaceutical requirements, and clinical requirements.(Amalia & Putri, 2021)

A. Drug-Related Problems

Drug-related problem is an unexpected situation related to the patient's drug therapy, resulting in the unaccomplished patient's therapy outcome. (Ahmed et al., 2021)

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DRP can be solved or prevented if the cause of the problem is clearly understood. Therefore, it is necessary to identify DRP and its causes. By identifying the cause, practitioners and patients concern about DRP so that patients are aware of the potential benefits of therapy.(Cipolle, 2004) Common categories and causes of DRP according to Cipolle et al. include unnecessary drug therapy, the need for additional drug therapy, improper medication, inadequate dosage, adverse drug reactions, excessive dose of medication, and patient non-compliance.

No.	Drug Related Problems	Causes of drug related problems
1.	Unnecessary drug therapy	Patients receive medication without clear medical indications Non-drug therapy is more suitable for patients Patients receive medication to address side effects due to medications that are actually preventable Patients with treatment problems related to drug abuse, alcohol, and cigarette use
2.	The need for additional drug therapy	Medical conditions that require new drug therapy The need for drug therapy as a prevention to reduce the risk of the emergence of a new disease A medical condition that requires additional drug therapy to achieve synergistic or additive effects
3.	Improper medication	Patients have a harmful risk to the medication they receive Improper form of preparation The medication needed for the patient is not the most effective cure for the disease he or she suffers from
4.	Inadequate dosage	Doses are too low to produce the desired response Drug levels in the blood are below the therapeutic range The frequency and duration of drug therapy that is too short to produce the desired response
5.	Adverse drug reactions	The use of the drug generates an undesirable response The bioavailability of drugs changes due to interaction with other drugs or with food The effects of the drug will change due to the induction or inhibition of enzymes by other drugs Rapidly changing use of medications Patients are allergic to the drug
6.	Excessive dosage of the drug	The drug dose is too high Frequency and duration of medication that is too long The level of the drug in the blood is above the therapeutic range Improper dose, duration, frequency, route of administration
7.	Compliance	Patients do not comply with the rules given for treatment Patients do not fill the prescription because the drugs are expensive Patients do not fill the prescription due to a lack of knowledge about medication use Patients fail to receive the right medication due to medication error

Table 1. Categories and Common Causes of Drug Related Problems (Cipolle et al., 2004)

Pharmacists are one of the pillars as a part of the prevention of DRP, especially when conducting prescription assessments (Batson et al., 2020). In the process of prescription assessment, pharmacists verify the potency, purity, stability and sterility of the drugs that will be prepared and given to patients. In addition, in prescription assessment, pharmacists also verify that the prescription includes the correct type of drug, dosage, regimen, route, and schedule. This includes dosage adjustments if there are special conditions in some organ functions (Holle et al., 2021). Based on a study conducted by Titiesari et al., clinical pharmacists reported 146 DRP reports related to cancer patients at a special cancer hospital from January to August 2021. The most common DRP problems were medication safety (63.7%) and treatment effectiveness (17.81%). The most common causes of DRP were drug selection (38.06%), drug dosage selection (21.94%), and duration of drug therapy (14.84%) (Titiesari et al., 2022)

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B. Cytotoxic Drug Reconstitution Guidance

Drug reconstitution is the process of mixing injectable drugs with sterile solutions to produce intravenous preparations that are ready for use and ensure the sterility of the product to be injected (*Kemenkes*, 2021). Cytotoxic or oncolytic substances are substances that can stop the rapid growth of malignant cells (Tjay, 2007). Cytotoxic drug reconstitution is the mixing of cytotoxic drugs with a specific required dose and then dissolving them into solvents and the concentration is according to the requirements.

Injectable cytotoxic drug compounding requires specific guidance regarding formulary restrictions, solvent type, solvent volume, dosage calculation, and drug stability. The guidance currently used include the National Formulary, Guidelines for Mixing Injectable Drugs and Handling Cytostatic Preparations, leaflets for each product, Handbook on Injectable Drugs, Drug Information Handbook, British Columbia Cancer Chemotherapy Preparation and Stability Chart, and Cancer Therapy Regimens 2023. The current references are not integrated and sometimes the information provided is different from one reference to another. Prescribers also have their own guidance that does not include all the information related to cytotoxic drugs and is sometimes different from the guidance used by the pharmaceutical department. This difference is one of the reasons for the occurrence of DRP and the prolonged prescription assessment duration.

C. Information Technology in Pharmaceutical Services

Information technology plays a significant role in the advancement of the pharmaceutical industry in particular and healthcare in general. A study conducted by (Mayasari, 2023) showed that the SiCALCA application (an application for measuring nutritional needs in pediatric cancer patients) functioned well and met expectations expectations.

A study conducted by Wien et al. on the use of the CPOP (Computerized Physician Order Entry) and CDSS (Clinical Decision Support System) systems in one of tertiary health care facilities in psychiatric patients shows that the use of these technology and information systems could reduce the incidence of DRP (Wien, 2024)

. A study conducted by (Neville et al., 2014) compares the duration required for prescription assessment until the drug is ready between the group that implements the Digital Scanning Technology (DST) system and the group without the system. The result of the study shows that the duration required from prescription assessment to the drug being ready for all treatments decreased significantly.

Materials And Methods

The study used an experimental study design, which compared the effect of differences in the implementation of cytotoxic drug reconstitution guidance on the DRP occurrence and the duration of assessment of the injection chemotherapy prescriptions in pediatric patients. The sample used was a prescription for chemotherapy injections in pediatric patients less than 18 years old, prescribed by the Junior Residents of PPDS (Specialist Doctors Education Program) and containing at least 2 cytotoxic drugs. The prescription used as a sample is also a prescription on the first day of 1 cycle, while the chemotherapy prescriptions after the first day of 1 cycle were not included in the sample.

The independent variable in this study was the cytotoxic drug reconstitution guidance system. The dependent variables were the percentage of DRP occurrence and the duration of prescription assessment. The control variables were the officers who performed the prescription assessment and the prescribing doctors. Sample data were collected using the purposive sampling method. In the first month, data on the occurrence of DRP and the duration of prescription assessment were collected without implementing an electronic-based cytotoxic drug guidance system with a total of 30 sample data as a control group. In the following month, data on the occurrence of DRP and the duration of prescription assessment were collected by implementing an electronic-based cytotoxic drug guidance

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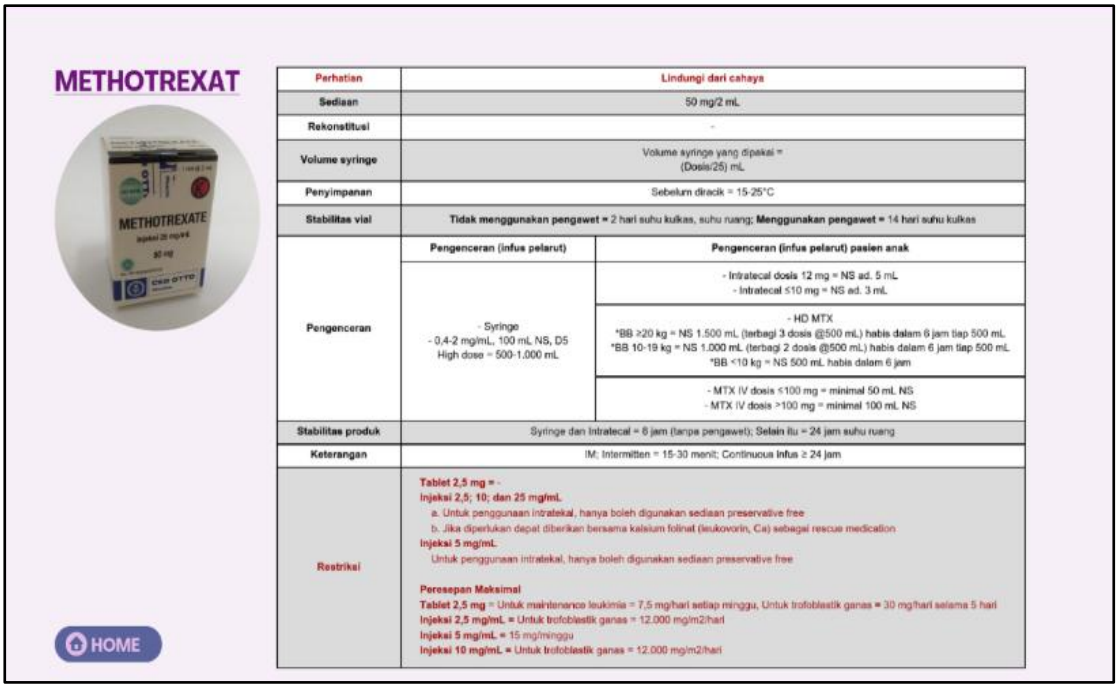
system with a total of 30 sample data as a treatment group. The analysis of the data obtained was conducted using statistical test. The test used for the normality test was the Kolmogorov – Smirnov test. If the data were distributed normally, then the difference test would be using the Independent Sample T Test. Meanwhile, if the data were not distributed normally, the difference test would be using Mann Whitney.

Results

1. Cytotoxic Drug Reconstitution Guidance System

The developed cytotoxic reconstitution guidance system (bit.ly/apotekudss) contains information about drug preparation, reconstitution procedures, solvent type and volume, storage temperature, stability, national formulary limitations, maximum dosage calculations, echocardiography scheduling for anthracycline drugs, drug interactions, and common errors in pediatric cytotoxic prescriptions.



Perhatian	Lindungi dari cahaya	
Sediaan	50 mg/2 mL	
Rekonstitusi	-	
Volume syringe	Volume syringe yang dipakai = (Dosis/25) mL	
Penyimpanan	Sebelum diracik = 15-25°C	
Stabilitas vial	Tidak menggunakan pengawet = 2 hari suhu kulkas, suhu ruang; Menggunakan pengawet = 14 hari suhu kulkas	
Pengenceran	Pengenceran (infus pelarut)	Pengenceran (infus pelarut) pasien anak
	- Syringe - 0,4-2 mg/mL, 100 mL NS, D5 High dose = 500-1.000 mL	- Intratecal dosis 12 mg = NS ad. 5 mL - Intratecal ≤10 mg = NS ad. 3 mL
		- HD MTX *BB ≥20 kg = NS 1.500 mL (terbagi 3 dosis @500 mL) habis dalam 6 jam tiap 500 mL *BB 10-19 kg = NS 1.000 mL (terbagi 2 dosis @500 mL) habis dalam 6 jam tiap 500 mL *BB <10 kg = NS 500 mL habis dalam 6 jam
		- MTX IV dosis ≤100 mg = minimal 50 mL NS - MTX IV dosis >100 mg = minimal 100 mL NS
Stabilitas produk	Syringe dan Intratecal = 8 jam (tanpa pengawet); Selain itu = 24 jam suhu ruang	
Keterangan	IM: Intermitten = 15-30 menit; Continuous infus ≥ 24 jam	
Restriksi	**Tablet 2,5 mg** = - **Injeksi 2,5; 10; dan 25 mg/mL** a. Untuk penggunaan intratekal, hanya boleh digunakan sediaan preservative free b. Jika diperlukan dapat diberikan bersama kalsium folinat (leukovorin, Ca) sebagai rescue medication **Injeksi 5 mg/mL** Untuk penggunaan intratekal, hanya boleh digunakan sediaan preservative free **Peresepan Maksimal** **Tablet 2,5 mg** = Untuk maintenance leukimia = 7,5 mg/hari setiap minggu, Untuk trofoblastik ganas = 30 mg/hari selama 5 hari **Injeksi 2,5 mg/mL** = Untuk trofoblastik ganas = 12.000 mg/m2/hari **Injeksi 5 mg/mL** = 15 mg/minggu **Injeksi 10 mg/mL** = Untuk trofoblastik ganas = 12.000 mg/m2/hari	

Table 2. Cytotoxic Drug Information

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PERHITUNGAN DOSIS MAKSIMAL*

(sesuai dengan Formularium Nasional 2023)

ISILAH DATA DI KOLOM BERWARNA KUNING !	**DATA PASIEN**		
	BB PASIEN	55.0	**kg**
	TB PASIEN	161.0	**cm**
	BSA (Body Surface Area)	1.6	**m²**
UNTUK OBAT CARBOPLATIN, ISI JUGA KOLOM BERWARNA BIRU BERIKUT !	Creatinin	0.8	**mg/dl**
	Tanggal lahir	3/5/1961	**tgl/bulan/tahun**
	Jenis Kelamin	P	**P/L**
UNTUK OBAT MESNA, ISI KOLOM BERWARNA UNGU BERIKUT !	Dosis ifosfamid (jika bersama ifosfamid)		**mg**
	Dosis cyclophospamid (jika bersama cyclophospamid)	750.0	**mg**

Nama Obat	Merk obat	Rumus	Dosis Maksimal	Satuan
Asparaginase	Leunase	-	-	**mg**
Bendamustin	Bentero, Foncomustin	CLL: 100 mg x BSA hari 1 dan 2 pada siklus 28 hari'	156.8	**mg**
		MM: 120-150 mg x BSA pada hari 1 dan 2	235.3	**mg**
Brentuximab vedotin	Adcetris	16 siklus	-	
Bleomycin	Bleocin	12 kali pemberian	-	**mg**
Bortezomib	Bortero, Fonkozomib	hari 1, 4, 8, 21, setiap siklus 3 minggu, maksimal 8 siklus	-	**mg**
Carboplatin		AUC 5-6	525.0	**mg**
Cisplatin		100 mg x BSA	156.8	**mg**
Cetuximab	Erbitux	Dosis pertama : 400 mg x BSA	627.3	**mg**
		Dosis selanjutnya : 250 mg x BSA	392.1	**mg**
Cyclophosphamide	Endoxan	-	-	**mg**
Cytarabine	Kabitarin	-	-	**mg**
Dacarbazine		12 kali pemberian	-	**mg**

Table 3. Calculation of Maximum Dosage

2. DRP Occurrences

The control group had 26 DRP occurrences and 20 DRP cases, while the treatment group had 6 occurrences and 6 cases.The Mann–Whitney test showed p = 0.000 (p < 0.05), indicating a significant difference between groups.

No	Type of DRP	Number	
		Control Group	Treatment Group
1	Unnecessary drug therapy	1	0
2	The need for additional drug therapy	2	0
3	Improper medication	0	0
4	Inadequate dosage of the drug	5	1
5	Adverse drug reactions	0	0
6	Excessive dosage of the drug	10	1
7	Compliance	0	0
8	Others (inadequate volume of solvent)	3	0
9	Others (excessive volume of solvent)	4	4
10	Others (the drug is already unstable)	1	0
	Total	26	6

Table 4. Table of Number of DRP Events by Type of DRP

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3. Duration of prescription assessment

The average assessment duration in the control group was 7 minutes 2 seconds, while in the treatment group it was 3 minutes 18 seconds. Statistical analysis showed a significant difference ($p < 0.05$).

No	Control Group			Treatment Group		
	Number of incomplete files	Number of DRP Occurrences	Duration of prescription Assessment	Number of incomplete files	Number of DRP occurrences	Duration of prescription Assessment (minutes:sec)
1	0	2	16:44	0	1	1:50
2	2	1	5:16	0	0	1:07
3	0	0	6:18	1	0	1:41
4	2	1	10:28	0	0	1:24
5	1	1	15:10	0	1	5:30
6	1	1	10:21	1	0	5:11
7	1	0	3:20	1	1	6:12
8	0	2	12:31	0	0	0:28
9	0	1	6:41	0	0	0:53
10	0	1	3:45	0	0	1:31
11	0	0	5:35	0	0	1:29
12	0	1	2:10	1	1	3:11
13	0	0	2:15	0	0	0:53
14	1	1	11:40	0	0	1:44
15	0	1	18:02	0	0	3:50
16	0	2	8:00	0	0	2:26
17	0	0	1:39	0	1	4:48
18	0	0	4:41	0	0	1:20
19	0	1	3:26	0	0	2:04
20	0	2	2:44	0	0	1:45
21	2	0	6:18	0	0	2:04
22	1	1	7:47	0	0	1:27
23	0	2	9:35	0	0	1:20
24	0	0	4:01	1	0	4:46
25	0	0	2:35	1	0	9:26
26	1	2	9:32	1	0	6:07
27	1	0	3:51	1	0	6:47
28	1	1	4:59	0	0	3:31
29	1	1	4:26	0	1	11:25
30	1	1	7:18	0	0	3:12
	Total: 16	Total: 26	Average: 7:02	Total: 8	Total: 6	Average: 3:18

Table 5. Duration of Prescription Assessment of Control and Treatment Groups

Discussion

1. Effect of the Guidance System on DRP Reduction

The guidance system reduced DRP occurrences from 26 to 6. This aligns with findings by (Wien, 2024), where CPOE and CDSS implementation significantly decreased DRP events in psychiatric patients ($p < 0.001$).

DRP types such as unnecessary therapy, inadequate or excessive dosage, and solvent errors occurred mainly because prescriptions were written by junior PPDS residents with limited chemotherapy experience.

The educational materials and dosage calculators within the guidance system helped prescribers better interpret chemotherapy protocols and avoid dosing errors.

Information on solvent type and volume also minimized instability and inappropriate concentrations that could lead to treatment complications.

2. Impact on Prescription Assessment Duration

The implementation of the guidance system shortened assessment time by more than half. This finding is consistent with (Neville et al., 2014)where digital scanning technology significantly reduced processing time from 2h 23m to 1h 33m.

Assessment time in some control samples remained long despite no DRP due to incomplete supporting files required for BPJS validation, such as pathology results, BMP, IHC, echocardiography, lab tests, or protocol documentation. The absence of these documents required manual checking in the e-MR, extending assessment time.

The treatment group still had slightly longer duration than experienced PPDS residents' prescriptions (average 2:28), but the improvement remains significant.

Conclusion

This study demonstrated that the implementation of an electronic-based cytotoxic drug reconstitution guidance system at Dr. Moewardi Hospital effectively reduced both the number of Drug-Related Problems (DRPs) in pediatric chemotherapy prescriptions and the duration of prescription assessment. These findings indicate that the system contributes to improving the safety and efficiency of chemotherapy services, addressing the previously identified problems of high DRP incidence and extended assessment time.

Although the results are promising, this study has limitations, including the relatively small sample size and the short observation period. Future research should involve larger and more diverse patient populations, evaluate long-term system performance, and explore user experience and system integration within broader clinical workflows. Such studies will help optimize the system and strengthen its contribution to medication safety in oncology settings.

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