Impact of Clinical Pharmacy Services in a Hematology/Oncology Inpatient Setting

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Abstract. *Background/Aim: Clinical pharmacists are contributing to safe medication use by providing comprehensive management to patients and medical staff. However, little is known regarding their impact in oncology. The aim of this study was to document and evaluate the role of clinical pharmacy services in a hematology/oncology department. Patients and Methods: A prospective, descriptive, observational study was carried out from May 2012 to May 2013. Medication reviews concerning hospitalized adult cancer patients were performed twice a week. Medication problems, pharmaceutical interventions and acceptance rate by the oncologists were recorded by a clinical pharmacist. Results: A total of 4,393 prescriptions (including chemotherapy and support) of 489 adult cancer patients (mean age=63 years) were analyzed. The pharmacist identified 552 drug-related problems (12.6% of the prescriptions) primarily related to anti-infective agents (59.5%). Medication problems included inappropriate medications (20.6%), untreated indications (14.8%), inappropriate administrations (14.1%), underdosing (11.7%), drug-drug interactions (14.3%), lack of monitoring (9.6%), overdosing (8.9%), administration omissions (3.5%) and side-effects (2.5%). Interventions (n=552) led to treatment discontinuation (26.2%), drug dosing adjustments (21.5%), drug additions (16.9%), alternate routes of administration (11.7%), replacement of a drug by another one (10.7%), therapeutic drug monitoring (10.3%) and optimizing administration (2.6%). Most (96%) of the interventions were accepted and implemented by the medical staff. Conclusion: The integration of clinical pharmacy services resulted in drug-specific interventions in 12.6 % of the prescriptions of hospitalized adult patients with cancer. Medication problems mostly concerned anti-infective agents. The intervention acceptance rate by oncologists was high. The outcome of care in the hematology/oncology inpatient setting remains to be measured.*

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Drug management of patients with cancer is complex because it integrates numerous agents (chemotherapy, supportive care and medications for co-morbidities). Furthermore, many anticancer drugs enter the market and some of them are characterized by a great potential of drug interactions and atypical side effects. Consequently, clinical pharmacists trained in oncology have an important role in securing the use of all these drugs through comprehensive medication reviews and information for the medical staff and patients (clinical pharmacy services) (1). Medication review focuses on the identification of drug-related problems that include inappropriate medications, inappropriate dosing and mode of administration, drug-drug interactions, drug omissions, lack of monitoring. To solve these problems, pharmaceutical interventions lead to drug dosing adjustments, treatment discontinuations, drug additions, replacement of a drug by another one. Among published studies in oncology, some have focused on the optimization of medications lists (2), the prevalence of drug-drug interactions or prescription duplications (3-6), the outpatient setting (7-9), the management of certain support therapies (10) or specific populations (types of cancer, elderly) (11,12). Paradoxically, published data, relative to clinical pharmacy services at large, in hospitalized patients with cancer are scarce (13).

The aim of this prospective study was to document and evaluate clinical pharmacy services in a hematology/oncology inpatient setting.

Patients and Methods

Setting and patients. This prospective, descriptive, observational study was carried out from May 2012 through May 2013 at the

Hematology/Oncology Department (52 beds, 3 wards) of Strasbourg University Hospital, a teaching hospital in France. The Department treats patients with solid tumors (except lung cancer) and hematological cancers, including those requiring high dose chemotherapy with hematopoietic stem cell transplantation. All adult patients (older than 18 years) with cancer hospitalized in the Department were considered for the study.

Data collection. Comprehensive medication reviews (chemotherapy, supportive care and ambulatory treatment) were performed twice a week (from Monday to Friday) by the clinical pharmacist integrated in the department. Following the analysis of the prescription, the clinical pharmacist identified medication problems: inappropriate medications, untreated indications, inappropriate administrations, under- or overdosing, drug-drug interactions, lack of monitoring, administration omissions and side effects. Subsequently, he made interventions relative to the choice of the medication, the indication, the dosing schedule, the drug-drug interactions, the drug omission, the lack of monitoring. Medication problems and interventions were defined according to the French Society of Clinical Pharmacy (Société Française de Pharmacie Clinique) (14). The classification of medical problems per therapeutic class was made according to the Anatomical Therapeutic Chemical Classification (ATC). Drug-drug interactions were analyzed according to the reference database of the French drug agency (Thésaurus des interactions médicamenteuses de l'Agence Nationale de Sécurité du Médicament et des Produits de santé) (15). The intervention acceptance rate by the oncologists was also evaluated.

Statistical analysis. Data were prospectively collected and analyzed with the use of Excel 2010. Descriptive statistics were used to describe frequency, type and classification of medication problems.

Results

During the study period, 4,393 prescriptions (including chemotherapy and support) of 489 adult cancer patients (mean age=63 years) were prospectively analyzed. The pharmacist identified 552 drug-related problems (12.6% of the prescriptions) primarily related to anti-infective agents (ATC class J: 327/531; 59.5%), drugs regarding the alimentary tract and metabolism (ATC A: 6.4%), dermatologicals (ATC D: 6.2%), drugs of the cardiovascular system (ATC C: 6%) and drugs of the nervous system (ATC N: 5.5%). Anticancer agents (ATC L) only represented 3.9% of drug-related problems.

Medication-related problems (Table I) included inappropriate medications (20.6%), untreated indications (14.8%), drug-drug interactions (14.3%), inappropriate administrations (14.1%), underdosing (11.7%), lack of monitoring (9.6%), overdosing (8.9%), administration omissions (3.5%) and side effects (2.5%).

Interventions (n=552) led to treatment discontinuations (26.2%), drug dosing adjustments (21.5%), drug additions (16.9%), alternate routes of administration (11.7%), replacement of a drug by another one (10.7%), therapeutic drug monitoring (10.3%) and optimizing administration (2.6%). Examples of interventions are shown in Tables II and III. Most (96%) interventions were accepted and implemented by the medical staff.

Table I. *Medications-related problems (n=552 among 4,393 prescriptions in 489 hospitalized adult cancer patients).*

Inappropriate medication	114 (20.6%)
Untreated indication	82 (14.8%)
Inappropriate administration	78 (14.1%)
Underdosing	65 (11.7%)
Drug-drug interactions	79 (14.3%)
Lack of monitoring	53 (9.6%)
Overdosing	49 (8.9%)
Administration omissions	19 (3.5%)
Side-effects	13 (2.5%)

Discussion

In this large prospective study, we found that comprehensive medication review by the clinical pharmacist resulted in the identification of drug-related problems in 12.6% of the prescriptions of 489 adult hospitalized patients with cancer. Most of the medication-related problems involved anti-infective agents, while very few concerned anticancer drugs. This is not surprising because hospitalized patients necessitate supportive care in relation with advanced disease (cancer symptoms), complications of cancer treatment and intensive chemotherapies for hematological cancers.

Overall, 20.6% of the interventions concerned inappropriate medications. Drug-drug interactions were reported in 14.3% of the interventions, representing 1.8% of the prescriptions. Untreated indications and inappropriate drugs were also the main drug-related problems identified in a small Swedish study that included 33 hospitalized patients with solid tumors (13). A Dutch study conducted in the outpatient setting reported a higher rate of medication problems (20%) in 4,618 prescriptions of a population of 546 patients receiving anticancer treatment (9). Drug-related problems mainly concerned contraindications (46.9%) and drug-drug interactions (44.4%) (6). Discrepancies may be imputable to differences in the classification of medical problems and the type of population (outpatient setting *versus* inpatient setting). Regarding drug-drug interactions, we report a lower rate of drug-drug interactions than Bulsink *et al*. (1.8% *versus* 9.1% of the prescriptions) (9). Higher rates of potential drug-drug interactions (27% - 58%) have been reported in more specific studies including ambulatory patients under intravenous anticancer treatment (4, 5). In all, our lower rate of drug-drug interactions may be explained by the fact that we intervene on major issues, using a different screening method, in a context of inpatient setting that allows enhanced and continuous monitoring.

Table II. *Examples of pharmaceutical interventions in the hematology/oncology setting.*

Classification of the intervention	Description of case	Pharmaceutical intervention	Resolution
Drug dosing adjustments	Prescribed for a febrile neutropenic patient with Klebsiella sp. pneumonia septicemia: IV imipenem/cilastatin 500 mg every 8 hours	Recommended dose of imipenem/ cilastatin: 2 g to 3 g per day	Changed to IV imipenem/ cilastatin 1 g every 8 h
	Prescribed for aspergilosis: oral voriconazole 400 mg every 12 hours	Overdosing: residual plasma concentration of voriconazole is 5.7 mg/l (usual values 1-4 mg/l)	Changed to oral voriconazole 300 mg every 12 h
	Prescribed oral nebivolol 30 mg once a day	Recommended maximal dose of nebivolol: 10 mg once a day	Changed to nebivolol 10 mg once a day
	Prescribed for an elderly patient: IV ofloxacin 200 mg every 12 hours. Patient with Clcr=37 ml/min	Recommended dose of ofloxacin for patients with Clcr <50 ml/min: half the dose	Changed to IV ofloxacin 200 mg once a day
Treatment discontinuations	Prescribed high dose of methotrexate for lymphoblastic leukemia and piperacillin/tazobactam for febrile neutropenia	Combination is not recommended: risk of toxicity due to delayed elimination of methotrexate by piperacillin/tazobactam	Stopped piperacillin/ tazobactam and changed to ceftriaxone
	Prescribed linezolide and tramadol	Contraindication: risk of serotonin syndrome	Stopped tramadol and changed to nefopam
	Prescribed high dose of methotrexate for T lymphoma and trimethoprim/ sulfamethoxazole for pneumocystis prophylaxis	Contraindication: risk of increased toxicity	Stopped trimethoprim/ sulfamethoxazole
	Prescribed oral lapatinib and the proton pump inhibitor esomeprazole	Decreased absorption of lapatinib	Stopped proton pump inhibitor

IV, Intravenous; Clcr, creatinine clearance.

Table III. *Examples of pharmaceutical interventions in the hematology/oncology setting.*

Classification of the intervention	Description of case	Pharmaceutical intervention	Resolution
Drug additions	Prescribed L-asparaginase for a acute lymphoblastic leukemia	Recommendation that for the prescription of L- asparaginase, a prophylaxis of thrombosis must necessary	Adding low molecular-weight heparin
Alternate routes of administration	Prescribed voriconazole IV since 72 h for aspergillosis. Patient is afebrile	The oral route is available	Changed to: oral voriconazole
Therapeutic drug monitoring	Prescribed high dose of methotrexate for Burkitt lymphoma	Methotrexate plasma concentration at the 48th h is not measured	Adding methotrexate plasma monitoring
	Prescribed vancomycin IV 2g per day for *Staphylococcus*. sp septicemia	Residual plasma concentration of vancomycin is low (6.7mg/l; usual residual value between 20-30mg/l)	Changed to: vancomycin IV 3g per day

IV, Intravenous; PO, orally; Clcr, creatinine clearance.

One limitation of our intervention is the fact that the clinical pharmacist is not present in the department during the week-end. For example, our experience reported a case of toxicity to high-dose methotrexate in a context of a preventable interaction with piperacillin/tazobactam occurring in a leukemic patient during a week-end (16). The patient had severe mucositis and headaches but the renal function was not altered. Toxic methotrexate serum concentrations were sustained for the week-end and were only abated on Monday with the discontinuation of the antibacterial agent by the clinical pharmacist. We, thus, had to inform all residents and oncologists of the department about the risks of drug-drug interactions with high-dose methotrexate.

Conclusion

The integration of a clinical pharmacist in an Oncology/ Hematology Department resulted in drug specific

interventions for 12.6% of the prescriptions of hospitalized adult patients with cancer. Almost all interventions were accepted by the oncologists. The impact, in terms of improved care, remains to be evaluated.

Conflicts of Interest

No conflicts of interest to declare.

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