

Review

New Anticancer Agents: Role of Clinical Pharmacy Services

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Abstract. *Clinical pharmacy (or clinical pharmacy services) aims to contribute to safe medication use by providing comprehensive management to patients and medical staff, both in the community and the hospital. In oncology, these services include comprehensive medication reviews integrating chemotherapy, supportive care and ambulatory treatment for co-morbidities, medication information for the medical staff and patients, therapeutic drug monitoring (anticancer agents, anti-infective agents, immunosuppressive drugs in recipients of allogeneic stem cell transplantation), supportive care counseling (nutritional support, pain management, chemotherapy side-effects prophylaxis and treatment), elaboration of therapeutic guidelines, optimal use of economic resources. With regard to new anticancer agents, pharmacists both in the community and in hospitals are faced with a growing body of complex information as well as the development of ambulatory treatment (oral agents, subcutaneous administration). Clinical pharmacists with oncology training have the potential to optimize drug use both in the hospital and the community. With the understanding and recognition of drug interactions and side-effects, pharmacists can provide timely interventions and information to health providers, as well as counseling to patients.*

From the pharmacist's point of view and when compared to other clinical disciplines, oncology is characterized by the rapid availability of numerous, costly anticancer agents with new mechanisms of action and sometimes very narrow

indications. Based on clinical trials registered between 2007 and 2010 on ClinicalTrials.gov, oncology represents the largest discipline (21.8% of the trials), followed by mental health (9%) and infectious diseases (8.3%) (1). In addition, among the drugs approved in 2012 (39 in the United States and 33 in the European Union), 25-33% were anticancer agents (13/39 in the United States; 8/33 in the European Union) (2). Another characteristic of oncology has been the development of oral chemotherapy, as well as the re-birth of the subcutaneous route offering patients a more convenient ambulatory management and the possibility of treatment at home (3). In this context of a fast-growing oncology drug market, both in the community and in hospitals, pharmacists are faced with complex and evolving information while they have to optimize and secure all these new therapies.

Clinical pharmacy (or clinical pharmacy services) aims to contribute to safe medication use by providing comprehensive management to patients and medical staff, both in the community and the hospital. Pharmacist intervention outcomes include medication appropriateness, adverse drug events, patient satisfaction and economics.

Clinical Pharmacy and Oncology

Clinical pharmacy, as a discipline, may not be known by all physicians but underlines the evolution of the profession of trained pharmacists from drug distribution and chemotherapy preparation to patient-centered services. Clinical pharmacy in oncology is not very well described; a PubMed search (January 5th, 2014) using the terms "clinical pharmacy services and oncology" only retrieves 229 articles since 1976. In oncology, these services include comprehensive medication reviews integrating chemotherapy, supportive care and ambulatory treatment for co-morbidities, therapeutic drug monitoring (anticancer agents, anti-infective agents, immunosuppressive drugs in recipients of allogeneic stem cell transplantation), supportive care counseling (nutritional support, pain management, chemotherapy side-effects, prophylaxis and treatment), medication information for the medical staff and patients including promotion of adherence to ambulatory

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treatments, elaboration of therapeutic guidelines, optimal use of economic resources (4) (Table I). Consequently, clinical pharmacists support the multidisciplinary management of patients with cancer.

Optimized medication review implies a comprehensive and accurate list of medications taken by the patient (prescription drugs and self-medication). Most cancer patients are aged above 65 years and often have other diseases. In hospitals, the review can be preceded by a phase called reconciliation, generally performed by pharmacists, which aims to identify and correct medication discrepancies during transition care, for example at admission (*i.e.* to verify that all the drugs taken by the patient at home have been integrated into the medical record by the oncologist). A study performed in the United States found that 24% of the prescription drugs from 152 patients undergoing chemotherapy in the clinic were missing in their medical records (5). Reconciliation can also be done at discharge because medication regimens might have change during hospitalization. To avoid any re-admission, it is important that patients understand these modifications before returning home (*i.e.* discontinue drugs that are no longer prescribed, for example). Far beyond the simple detection of drug–drug interactions, medication review focuses on the identification of medication problems (or drug-related problems). Medication problems include inappropriate medications, inappropriate dosing and mode of administration, drug–drug interactions, drug omissions, lack of monitoring. To solve these problems, pharmaceutical interventions, generally, lead to drug dosing adjustments that may be optimized in certain cases by the use of pharmacogenomics and therapeutic drug monitoring, treatment discontinuations, drug additions and replacement of one drug by another. In our experience, in a population of 212 adult hospitalized cancer patients (2,572 prescriptions including chemotherapy and support), the integration of clinical pharmacy services resulted after medication review in drug-specific interventions for 10% of the prescriptions (6). Overall, 20% of the interventions concerned inappropriate medications. Drug–drug interactions were reported in 10% of the interventions (representing 1% of the prescriptions). Most of the interventions concerned anti-infective agents and the intervention acceptance rate by oncologists was high (97%). A Dutch study reported a higher rate of medication problems (20%) in a population of 546 patients receiving anticancer treatment. Drug problems mainly concerned contraindications and drug–drug interactions (7).

Although the intervention of a clinical pharmacist appears beneficial for the cancer patient in the clinic, their value in terms of improved care has not been evaluated in a randomized trial (8). Research is, therefore, required to better understand the role of clinical pharmacy services in oncology. Further research also focuses on the improvement of pharmaceutical interventions and encompasses many areas

of therapeutics and pharmacology. For example, it includes the integration of pharmacogenomics data such as in acute lymphoblastic leukemia where cancer and germline genomics have proved to guide the treatment (9). It also focuses on the detection and prevention of drug interactions (with concomitant drugs, food and beverages, benefiting from the development of molecular pharmacokinetics and the availability of updated regulatory guidances for industry (Table II) (10).

Clinical Pharmacy and New Anticancer Agents

The research of new anticancer agents follows different approaches such as the continuation of classic cytotoxic drugs and endocrine therapies (eribulin, abiraterone, enzalutamide), the development of analogs and new formulations (vinflunine, cabazitaxel, pixantrone, pomalidomide, subcutaneous trastuzumab, liposomal vincristine), and targeted therapy. Most of the new anticancer agents are ‘targeted therapies’ or, in other words, drugs whose development is based on a pre-determined tumoral or endogenous target. These drugs are either monoclonal antibodies that interact with cell membrane receptors or circulating ligands or protein/enzyme inhibitors that interfere with various tumoral signaling pathways (11, 12). Monoclonal antibodies are injected intermittently by the intravenous or subcutaneous route, while the protein/kinase inhibitors are mostly administered chronically by the oral route. For clinical pharmacists, these new entities deserve renewed attention. Oral agents are subject to drug–drug interactions both as victims but also as perpetrators in relation to their chronic administration.(13). Furthermore, the development of oral/subcutaneous treatment for ambulatory patients require counseling for optimal compliance. Targeted agents display new mechanisms of action that generate unusual side-effects and novel supportive-care measures, including prevention and the intervention of collaborating specialists (cardiologists, dermatologists). In addition, some agents have narrow indications that are prone to off-label use (14). In all, clinical pharmacists have a role in the monitoring of new anticancer agents. Among others, we focus on medication problems and pharmaceutical interventions related to oral agents and unusual side-effects (Table III).

Oral agents. More than 60 oral anticancer agents are now available and among them, 22 kinase inhibitors have been approved worldwide since 2001 (imatinib). Contrasting with previous oral cytotoxic agents (idarubicin, fludarabine, cyclophosphamide, procarbazine), kinase inhibitors display a higher risk of drug–drug interactions because they are almost both substrates and inhibitors of major pharmacokinetic determinants (cytochrome *P450 3A4* or *CYP3A4*, p-glycoprotein or P-gp) and they are administered

Table I. *Clinical pharmacy services in oncology.*

Medication review with reconciliation (admission, hospitalization, discharge), integrating anticancer treatment, supportive care, ambulatory treatment, self medication
Drug use optimization integrating genomics and characteristics of the patient
Drug dosing optimization integrating therapeutic drug monitoring (anti-infective agents, anticancer agents, immunosuppressive drugs in recipients of allogeneic stem cell transplantation), pharmacogenomics and body size considerations
Medical staff and patient information and counseling, promotion of adherence to ambulatory treatments
Elaboration of therapeutic guidelines
Optimal use of economic resources

Table II. *Clinical pharmacy: Research in oncology.*

Impact of clinical pharmacy services in terms of clinical improvement, patient satisfaction and compliance in the clinic and in the community
Evaluation of activity and tolerance of new anticancer agents in real-life studies
Patterns of use of supportive-care drugs (antibacterial agents, antifungal agents)
Development and integration of measures of supportive care
Evaluation and analysis of off-label use of anticancer agents
Analysis of unexpected severe side-effects or low efficacy
Exploration of drug interactions (with food, beverages, concomitant drugs)
Development and integration of therapeutic drug monitoring and pharmacogenomics in drug use optimization
Impact of body size on pharmacokinetic and clinical variability of anticancer agents
Pharmacoeconomical studies

Table III. *Examples of medication problems and pharmaceutical interventions with new anticancer agents.*

Oral agents and drug interactions: promote accurate, exhaustive medication review
High risk of drug–drug interactions with kinase inhibitors and abiraterone (as substrates and perpetrators)
High risk of drug–drug interactions with enzalutamide (inducer of CYP3A4, CYP2C9, CYP2C19, CYP1A2, UGT, P-gp, BCRP, OATP1B1) in metastatic castration-resistant prostate cancer
High risk of toxicity when pomalidomide is given with macrolides (CYP3A/P-gp inhibitors) or ciprofloxacin (CYP1A2 inhibitor) in patients with myeloma with bacterial infection
Increased risk of QT prolongation and sudden death when nilotinib is given with food
Decreased oral absorption when erlotinib, gefitinib, dasatinib, sorafenib, bosutinib, vismedogib are administered with pH modifiers
Unusual side-effects
Skin toxicity with epidermal growth factor receptor antagonists (promote pre-emptive treatment)
Cardiovascular toxicity with antiHER2 agents, antiangiogenic agents, tyrosine kinase inhibitors (promote vigilance, monitoring)
Hypertension, proteinuria, thrombotic events, hemorrhage, gastrointestinal perforation with antiangiogenic agents (promote vigilance, monitoring and contraindications)
Hypothyroidism with sunitinib (promote monitoring)
Hepatotoxicity with the off-label association vemurafenib and ipilimumab in patients with metastatic melanoma (in a general way, promote vigilance with off-label combinations of new agents)

chronically (13). They can generate drug–drug interactions both as substrates and active agents. This also applies to abiraterone, a CYP3A substrate and a CYP2D6, CYP2C8 inhibitor which is used in the treatment of metastatic castration-resistant prostate cancer (15). Interactions with food, beverages (fruit juices), and pH modifiers may also occur, leading to variations in intestinal absorption. Fortunately, these interactions may be prevented due to better

documentation. This information followed new regulatory guidance and is included in the package insert. However, pharmacists should be aware of the risk of interactions with these new oral agents and should provide appropriate information to the oncologist and to the patients. For example, nilotinib must be taken without food because the ingestion of a high fat meal greatly increases the oral absorption (+50%) in patients with cancer, leading to a risk

of prolongation of the electrocardiographic QT interval and sudden death (16). Overexposure also occurs (ten-fold) when abiraterone acetate (the oral pro-drug of abiraterone) is taken with food (15). Furthermore, it underlines the debatable strategy of labeling these poorly-absorbable drugs in the fasted state (17). Pomalidomide is a new oral immunomodulatory agent used in the treatment of refractory myeloma. Contrasting with its analogs lenalidomide and thalidomide, pomalidomide pharmacokinetics are subject to P-gp and CYP3A4/CYP1A2 inhibition (18). Based on a randomized clinical trial, the use of pomalidomide combined with low-dose dexamethasone was characterized by a significant incidence of febrile neutropenia (10%) and pneumonia (12%) (19). Certain anti-bacterial agents are CYP1A2 inhibitors (ciprofloxacin) or CYP3A/P-gp inhibitors (macrolides except spiramycin). Giving pomalidomide with these antibacterial agents may be contraproductive since it can exacerbate the severity of infection. The oral absorption of some kinase/protein inhibitors (erlotinib, gefitinib, dasatinib, sorafenib, bosutinib, vismodegib) is decreased with concomitant administration of pH modifiers (proton pump inhibitors, H₂-receptor antagonists, antacids). Elevated gastric pH causes decreased solubility and impairs absorption (20). This interaction is of importance given the high prevalence of pH modifiers use among cancer patients. Based on two healthcare databases, a study has estimated that 20-33% of patients with cancer in the United States received a pH modifier, mostly a proton pump inhibitor (21). Enzalutamide is a new oral anti-androgen agent which is approved for treatment of metastatic castration-resistant prostate cancer. According to the package insert, enzalutamide is an inducer of many enzymes (CYP3A4, CYP2C9, CYP2C19, CYP1A2, UDP-glucuronosyltransferase or UGT) and drug transporters (P-gp, Breast Cancer Resistance Protein or BCRP, Organic Anion Transporting Polypeptide 1B1 or OATP1B1) (22). Enzalutamide has the potential to alter the pharmacokinetics of numerous co-administrated drugs. The risk of drug-drug interactions is huge and necessitates a careful and exhaustive medication review. Enzalutamide is added to the limited list of inducers including rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, efavirenz, mitotane and bosentan.

Side-effects. When compared to conventional chemotherapy, targeted-therapies differ in their pattern of side-effects. These toxicities, whose origins are related to the mechanisms of action (on/off target) or remain unknown, can impact on the patient's quality of life and lead to treatment discontinuation. Kinase inhibitors are often and erroneously considered as safe medications. On October 31, 2013, in the US the FDA suspended the marketing of ponatinib (initially approved in December 2012) used in the treatment of chronic myelogenous leukemia and Philadelphia-positive acute

lymphoblastic leukemia-intolerant or- resistant to prior kinase inhibitor therapy patients, due to life-threatening blood clots and severe narrowing of blood vessels. This severe side-effect occurred in 11.8% of the patients included in a phase II trial over a follow-up period of two years (23). For the first time, a kinase inhibitor was withdrawn from the market for toxicities reasons. The FDA announced on December 20, 2013 that the marketing of ponatinib could be resumed to a narrower population (those with resistance mutation T315I, that is to say 20% of the target mutations or for whom no other kinase inhibitor is appropriate) integrating new safety measures (24). In a general way, this emphasizes the reinforcement of vigilance for rapidly approved agents.

Drugs interacting with epidermal growth factor receptor (cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, afatinib) induce various dermatological side-effects (acneiform skin rash, xerosis, pruritus, paronychia, hair change) in more than 70% of the patients (25). These effects can be partially prevented (50% reduction) by the use of tetracyclines (doxycycline), sunscreen, topical steroids, skin moisturizer (26).

Cardiac events (hypertension, heart failure, left ventricular dysfunction, QT prolongation, thrombotic events) are reported in patients treated by bevacizumab, trastuzumab and some kinase inhibitors (sorafenib, sunitinib, pazopanib, cabozantinib, dasatinib, nilotinib, vandetanib) (27, 28). For example, heart failure or left ventricular dysfunction have been reported in 6% of patients under sunitinib (28). These cardiac side-effects may be exacerbated when kinase inhibitor agents are given with CYP3A inhibitors and/or food (nilotinib). In collaboration with oncologists and cardiologists, clinical pharmacists have a role in the prevention and the monitoring of side-effects through medication reviews and biological surveillance (check for preventive treatments and conditions that increase the risk of cardiac side-effects, such as other QT prolonging agents or drugs that lower plasma potassium and magnesium). Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF), a circulating pro-angiogenic factor. Bevacizumab is indicated in the treatment of various types of solid cancers and its use is associated with numerous side-effects: hemorrhage, hemoptysis, thrombotic events, hypertension, proteinuria, gastrointestinal perforations, stroke, cardiac events, wound-healing complications. Under real life conditions, these side-effects affected 30% of elderly patients. Moreover, 35.5% of the elderly patients under bevacizumab had a contraindication to the treatment (29).

Hypothyroidism is a frequent side-effect of sunitinib and has been observed in up to 85% of patients. Monitoring for hypothyroidism is required and may necessitate substitution therapy (30).

Ipilimumab and vemurafenib are both approved as single-agents in the treatment of metastatic melanoma. Based on their modest activity and their different mechanisms of

action, their association was evaluated in a phase I trial. Unfortunately, the study was closed due to liver side-effects (31). In a general way and beyond cost considerations (26,000 euros per month for the association), this must reinforce vigilance in the case of off-label association even if pre-clinical data are favourable (32).

Conclusion

Clinical pharmacists with oncology training have the potential to optimize the use of new anticancer agents both in the hospital and the community. With the understanding and recognition of drug interactions and side-effects, pharmacists can provide timely interventions and information to health providers, as well as counseling to patients. Further research is required to evaluate their influence in terms of improved care in randomized trials.

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