

Editorial

Drug interactions in cancer patients: A hidden risk?

Drug combinations with the potential to interact comprise an important but rather neglected topic in clinical cancer research. While several studies have evaluated drug interactions in general medicine, and the potential risks for patient's safety are well discussed, only few have addressed this subject in patients with cancer. Given the often large, and frequently increasing, number of drugs that cancer patients take, drug-drug interactions (DDIs) may pose a real threat of undesired adverse events, of increased or decreased efficacy of antineoplastic agents and may ultimately impact on patients' quality of life.

DDI is defined as an increase or decrease in the clinical effect of a certain drug due to interference by another drug.^[1] Patients with cancer are particularly susceptible to DDIs because they frequently take many medications besides antineoplastic agents, such as drugs to treat comorbidities, to relieve symptoms from cancer, and to treat cancer treatment-induced adverse events. In addition, the pharmacokinetic parameters of many drugs may be altered because of impaired absorption due to mucositis and diarrhea, increased volume of distribution resulting from edemas, and altered metabolism secondary to liver and/or renal dysfunctions.

Despite being generally acknowledged that DDIs may harm patients, their frequency in oncology is still high.^[1] Studies in general medicine have found frequency of potential drug interactions ranging from 16% in patients in emergency rooms to 70% in ambulatory patients.^[2] In oncology patients, several studies conducted by our group found that approximately 30% of overall cancer patients are at a risk of DDIs. A cross-sectional study of 405 ambulatory patients receiving systemic anticancer therapy found that at least one potential interaction was identified in 27% of them.^[2] Another study reported potential drug interactions in 63% of 100 hospitalized patients not receiving anticancer therapy.^[3] Among cancer patients receiving supportive care exclusively, potential drug interactions were identified in 31% of patients.^[4] A recent prospective study with ambulatory cancer patients also found clinically relevant DDI in 27% of cases.^[5] Risk factors for potential DDI include, as one would expect, number of medications, older age (likely because of more comorbid illnesses among the elderly), and patients with brain tumors.^[1] Such higher risk

groups reflect specific medication profiles associated with DDI such as drugs to treat comorbidities such as antihypertensives, warfarin, and anticonvulsants.^[1] Physician awareness of these potential DDI is crucial to avoid unnecessary harm to patients.

However, although the risk of DDI is generally recognized, the frequency of real DDI in oncology has not yet been elucidated. In a retrospective Norwegian study,^[6] 4% of deaths in hospitalized cancer patients were associated with severe drug interactions. In a study conducted by our group, 2% of 458 unplanned hospital admissions were deemed to be caused by a real DDI, mainly as a result of interactions with warfarin, antihypertensive agents, and phenytoin.^[7] This low frequency is likely underestimated because DDI may occur unrecognized. Real DDI may also have a great economic impact because they may not only lead to hospital admissions, but also prolonged and critical hospitalizations, multiple blood tests and other invasive procedures, and medications to treat new symptoms and complications.

The question about the best way to prevent DDI in oncology patients has yet to be answered. One approach is to screen patients at greater risk of DDI, such as those with many comorbidities and those utilizing antihypertensives, warfarin, and anticonvulsants. If feasible, physicians should substitute risky drugs to safer alternatives. For example, low molecular weight heparins do not interact with liver CYP enzymes and could be a safer option to warfarin as anticoagulants; in contrast with most tricyclic antidepressants, escitalopram does not interact with most cancer drugs. Other strategies include the use of electronic alerts for potentially hazardous combinations when physicians type patients' medication orders into electronic prescription programs, standardized institutional screening policies for DDI involving multidisciplinary teams such as doctors, nurses, and clinical pharmacists, increasing physician awareness (for example, during clinical rounds) and finally, educate patients. Patients could be educated by the health professional team about adverse events they may expect from certain combinations, to avoid herbs and over-the-counter medications without discussing them with their doctors, and being oriented to avoid certain foods and beverages known

to interact with drugs (e.g., grapefruit and its derived beverages). These simple interventions could be the key to avoid dangerous drug combinations.

In summary, the exponential growth in the number of new treatment options in oncology is likely to make DDI an even more frequent threat. The knowledge of potential drug interactions in patients that commonly are exposed to polypharmacy, and the development of institutional strategies to minimize these hidden risks are necessary to prevent damage to patient's wellbeing. Future studies should focus on better identification of real DDI and to develop prevention strategies to minimize the risk of DDI.

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