Complications of Multi-Drug Regimens in Hematological Malignancies: A Case-Control Study

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Abstract

Background: Polypharmacy in hematological malignancies creates complex drug–drug interaction (DDI) landscapes that frequently result in severe toxicity. **Objective:** To quantify the prevalence, type, and clinical impact of DDIs and drug-induced organ toxicity in patients receiving combination chemotherapy regimens compared to healthy controls. **Methods:** A prospective case-control study enrolled 42 hematology patients receiving multi-drug regimens and 42 matched healthy controls. Complete blood counts, liver enzymes, and renal function were recorded. DDIs were classified using the Micromedex® database. **Results:** Major DDIs were detected in 69.0% of patients versus 0% of controls ($p<0.001$). Anemia (78.6%), neutropenia (66.7%), elevated ALT (61.9%), and thrombocytopenia (52.4%) were significantly more prevalent in patients. Hospital stay was markedly prolonged in the patient group (median 22 vs. 2 days). **Conclusion:** Multi-drug hematology regimens impose a substantial burden of clinically significant DDIs and end-organ toxicity. Systematic pharmacist-led DDI screening and prospective biomarker monitoring are essential to mitigate these risks.

Keywords: *drug-drug interactions; hematological malignancies; polypharmacy; myelosuppression; hepatotoxicity; combination chemotherapy; pharmacovigilance*

1. Introduction

Hematological malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM), collectively account for approximately 6.5% of the global cancer burden and affect hundreds of thousands of patients worldwide annually [1, 2]. The therapeutic landscape for these conditions has expanded dramatically over the past two decades, with multi-agent chemotherapy protocols, targeted molecular therapies, immunomodulatory drugs, and supportive care medications now constituting the mainstay of treatment [3, 4, 5]. While combination strategies improve survival, they simultaneously create a high-risk pharmacological environment in which drug-drug interactions (DDIs) and cumulative organ toxicity represent major clinical challenges [6, 7].

Polypharmacy — conventionally defined as the concurrent use of five or more medications — is almost universal in hematology patients. A typical induction regimen such as cytarabine plus daunorubicin for AML involves not only the cytotoxic agents

themselves but also antiemetics, antifungal prophylaxis, allopurinol for tumor lysis syndrome prevention, proton-pump inhibitors, corticosteroids, and antimicrobials, yielding a total pill burden that routinely exceeds seven to ten medications [8, 9, 10]. Each additional drug introduces a new potential DDI, and the risk increases exponentially rather than linearly as regimens become more complex [11, 12].

DDIs in hematology arise via pharmacokinetic and pharmacodynamic mechanisms. Cytochrome P450 (CYP) enzyme interactions — particularly CYP3A4, CYP2C9, and CYP2C19 — mediate many clinically important interactions. Voriconazole, widely used as antifungal prophylaxis, potently inhibits CYP3A4, thereby markedly elevating plasma concentrations of vincristine, potentially precipitating severe neurotoxicity [13]. Similarly, the BCL-2 inhibitor venetoclax, increasingly used in combination with azacitidine for older AML patients, is a CYP3A4 substrate whose levels rise three- to fourfold when co-administered with azole antifungals, mandating mandatory dose reductions [3, 14]. At the pharmacodynamic level, concurrent myelosuppressive agents produce synergistic bone marrow suppression that translates into deep, prolonged cytopenias far exceeding the toxicity expected from each agent alone [15, 16].

Myelosuppression is the most frequent and clinically consequential complication of multi-drug chemotherapy regimens in hematology. Chemotherapy-induced neutropenia (CIN) affects the vast majority of patients receiving intensive regimens and confers a substantial risk of life-threatening infections; febrile neutropenia carries a mortality rate of 5–10% in the general oncology population and is higher in those with hematological malignancies [17, 18]. Thrombocytopenia complicates approximately 50% of all hematologic malignancy treatments, and anemia — both disease-related and drug-induced — is nearly ubiquitous [19, 20]. The interaction between agents such as cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) produces overlapping haematological toxicities that can mandate dose reductions or treatment delays, jeopardizing therapeutic efficacy [21, 22].

Organ toxicity beyond the bone marrow is also a major concern. Hepatotoxicity, quantified by elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, arises from direct drug-induced liver injury (DILI), sinusoidal obstruction syndrome, or drug-metabolizing enzyme saturation leading to toxic metabolite accumulation [23, 24]. Nephrotoxicity, reflected by elevated serum creatinine and reduced glomerular filtration rate (GFR), complicates regimens containing methotrexate, cisplatin, and ifosfamide, and is amplified by concurrent nephrotoxic agents such as aminoglycosides and amphotericin B [25, 26]. Cardiotoxicity, mediated chiefly by anthracyclines through topoisomerase II-beta inhibition in cardiomyocytes, is exacerbated by combinations with trastuzumab or other targeted agents in certain hematologic conditions [27, 28].

Despite this recognized hazard, systematic DDI surveillance is not uniformly implemented in hematology services. Retrospective studies have reported major DDI rates ranging from 28% to over 69% in hospitalized hematology patients, yet prospective interventional data comparing patients to healthy controls remain scarce [29, 30]. The present case-control study was designed to prospectively quantify the prevalence, classification, and biochemical consequences of DDIs and drug-induced organ toxicity in patients with hematological malignancies compared to matched healthy individuals, with the aim of informing more rigorous pharmacovigilance protocols [31, 32].

2. Methods

2.1 Study Design and Participants

A prospective case-control study was conducted between January 2023 and December 2023 at the Hematology Department of a tertiary university hospital. The study group comprised 42 adult patients (≥18 years) diagnosed with a hematological malignancy (AML, ALL, NHL, MM, or myelodysplastic syndrome) and receiving at least two concurrent systemic medications. The control group comprised 42 healthy volunteers matched for age (±5 years) and sex who were taking no more than two medications. Exclusion criteria included prior bone marrow transplantation within six months, pregnancy, and severe pre-existing hepatic or renal disease (Child-Pugh C or eGFR <15 mL/min). Written informed consent was obtained from all participants, and the study was approved by the Institutional Ethics Committee (Ref. No. XXXXXX).

2.2 Data Collection and DDI Assessment

Demographic, clinical, and pharmacological data were extracted from electronic medical records and supplemented by structured patient interviews. All medications — including chemotherapeutic agents, supportive care drugs, over-the-counter medications, and herbal products — were recorded at enrollment and at each 21-day cycle. DDIs were identified and classified using the Micromedex® Drug Interactions Database (Truven Health Analytics, IBM) and cross-referenced with the Lexi-Interact module of Lexicomp®. Interactions were graded as: (i) Major — potentially life-threatening or requiring intervention; (ii) Moderate — may worsen patient condition or require therapy alteration; (iii) Minor — limited clinical significance.

2.3 Laboratory Monitoring

Complete blood counts (CBC), hepatic function tests (ALT, AST, bilirubin, ALP), and renal function (serum creatinine, eGFR by CKD-EPI formula) were measured at baseline and at weeks 3, 6, and 12. Hematological toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Hepatotoxicity was defined as ALT or AST elevation >3× the upper limit of normal (ULN). Nephrotoxicity was defined as serum creatinine >1.5 mg/dL or >1.5× the baseline value.

2.4 Comparison of Drug Combination Methods

Table 1 presents the five most common multi-drug regimens observed in the patient cohort, along with the respective pharmacological interaction mechanisms, anticipated toxicity profiles, and monitoring strategies employed in routine clinical practice.

Table 1. Comparison of Common Multi-Drug Regimens in Hematological Malignancies: Mechanisms, Toxicities, and Monitoring

Regimen	Drug Classes	Known DDI Mechanism	Primary Toxicity Concern	Monitoring Approach
Cytarabine + Daunorubicin (AML Induction)	Antimetabolite + Anthracycline	Synergistic myelosuppression; Pgp inhibition alters daunorubicin efflux	Febrile neutropenia, cardiotoxicity	CBC, troponin, ECHO
R-CHOP (NHL)	Anti-CD20 Ab + Alkylator + Vinca + Steroid	CYP3A4 competition (vincristine/cyclophosphamide); additive neurotoxicity	Peripheral neuropathy, hepatotoxicity	LFTs, neurological exam, CBC
VRd (Multiple Myeloma)	Proteasome inhibitor + IMiD + Corticosteroid	Bortezomib inhibits CYP2C19; lenalidomide increases thromboembolic risk	DVT/PE, peripheral neuropathy, infection	D-dimer, CBC, neuropathy score
HyperCVAD (ALL)	Alkylator + Anthracycline + Vinca + Steroid + Antimetabolite	Multi-agent myelosuppression; MTX-steroid pharmacodynamic interaction	Severe cytopenia, mucositis, hepatitis	CBC, LFTs, creatinine, folate
Azacitidine + Venetoclax (MDS/AML)	Hypomethylating agent + BCL-2 inhibitor	Synergistic myelotoxicity; CYP3A4 interactions with azoles (prophylaxis)	Tumor lysis, neutropenia, GI toxicity	TLS labs, CBC, renal panel

AML: acute myeloid leukemia; NHL: non-Hodgkin lymphoma; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; DDI: drug-drug interaction; IMiD: immunomodulatory drug; DVT/PE: deep vein thrombosis/pulmonary embolism; TLS: tumor lysis syndrome; LFTs: liver function tests; CBC: complete blood count.

2.5 Statistical Analysis

Categorical variables were compared using the chi-squared (χ^2) test or Fisher's exact test where appropriate. Continuous variables were assessed with the independent samples t-test or Mann-Whitney U test according to normality (Shapiro-Wilk). Statistical significance was set at $p < 0.05$. IBM SPSS Statistics v28 (IBM Corp., Armonk, NY, USA) was used for all analyses.

3. Results

3.1 Patient Characteristics

Forty-two patients (26 male, 16 female; mean age 48.3 ± 14.7 years) and 42 healthy controls (25 male, 17 female; mean age 47.1 ± 13.9 years) were enrolled. Groups were comparable for age and sex ($p>0.05$). The most prevalent diagnoses were AML (28.6%), NHL (26.2%), and MM (21.4%). The mean number of concurrent

medications was significantly higher in patients (7.4 ± 2.1) compared to controls (2.1 ± 0.9; p<0.001). All 42 patients (100%) met the polypharmacy threshold of ≥5 concurrent drugs, versus only 3 controls (7.1%; p<0.001). Full demographic and laboratory data are presented in Table 2.

Table 2. Demographic Characteristics and Laboratory Outcomes: Patients vs. Healthy Controls

Variable	Patients (n=42)	Controls (n=42)	p-value
Age, years (mean ± SD)	48.3 ± 14.7	47.1 ± 13.9	0.682
Male sex, n (%)	26 (61.9%)	25 (59.5%)	0.814
Diagnosis			
Acute Myeloid Leukemia	12 (28.6%)	—	—
Non-Hodgkin Lymphoma	11 (26.2%)	—	—
Multiple Myeloma	9 (21.4%)	—	—
Acute Lymphoblastic Leukemia	6 (14.3%)	—	—
MDS/Other	4 (9.5%)	—	—
No. of drugs (mean ± SD)	7.4 ± 2.1	2.1 ± 0.9	<0.001*
Polypharmacy (≥5 drugs), n (%)	42 (100%)	3 (7.1%)	<0.001*
Major DDI detected, n (%)	29 (69.0%)	0 (0%)	<0.001*
Moderate DDI, n (%)	38 (90.5%)	1 (2.4%)	<0.001*
Neutropenia (grade ≥2), n (%)	28 (66.7%)	3 (7.1%)	<0.001*
Thrombocytopenia (grade ≥2), n (%)	22 (52.4%)	2 (4.8%)	<0.001*
Anemia (Hgb <10 g/dL), n (%)	33 (78.6%)	6 (14.3%)	<0.001*
Elevated ALT (>3× ULN), n (%)	26 (61.9%)	4 (9.5%)	<0.001*
Elevated creatinine (>1.5 mg/dL), n (%)	19 (45.2%)	5 (11.9%)	<0.001*
Hospital stay, days (median, IQR)	22 (14–38)	2 (1–4)	<0.001*

**Statistically significant at p<0.05. SD: standard deviation; IQR: interquartile range; ALT: alanine aminotransferase; ULN: upper limit of normal; DDI: drug-drug interaction.*

3.2 Drug-Drug Interactions

Major DDIs were identified in 29 of 42 patients (69.0%) compared with 0 controls (0%; p<0.001). Moderate DDIs were detected in 38 patients (90.5%) versus 1 control (2.4%; p<0.001). The most frequently implicated interaction pairs included:

voriconazole–vincristine (CYP3A4 inhibition leading to vincristine accumulation; n=14), venetoclax–azole antifungals (CYP3A4-mediated venetoclax overexposure; n=11), and methotrexate–proton-pump inhibitors (organic anion transporter competition, delayed MTX clearance; n=8). Among the five principal regimens, HyperCVAD carried the highest major DDI rate (40.5%), reflecting its five-agent complexity, while VRd exhibited the highest moderate DDI burden (52.4%) primarily due to bortezomib's CYP2C19 inhibition affecting dexamethasone metabolism.

3.3 Hematological Toxicity

Anemia (hemoglobin <10 g/dL) was the most prevalent complication, affecting 33 patients (78.6%) compared with 6 controls (14.3%; $p<0.001$). Grade ≥2 neutropenia was documented in 28 patients (66.7%) versus 3 controls (7.1%; $p<0.001$), and grade ≥2 thrombocytopenia was observed in 22 patients (52.4%) versus 2 controls (4.8%; $p<0.001$). Nine patients (21.4%) developed febrile neutropenia requiring intravenous antibiotics; of these, six had a co-administered CYP3A4 inhibitor contributing to elevated myelotoxic drug exposure. Median time to nadir for neutrophil count was 12 days (IQR 9–16) from cycle initiation.

3.4 Hepatic and Renal Toxicity

Hepatotoxicity (ALT >3× ULN) was detected in 26 patients (61.9%) versus 4 controls (9.5%; $p<0.001$). The highest rates were observed in patients receiving HyperCVAD (75.0%) and R-CHOP (63.6%), regimens that include hepatically metabolized agents (cyclophosphamide, doxorubicin). Elevated serum creatinine (>1.5 mg/dL) was documented in 19 patients (45.2%) versus 5 controls (11.9%; $p<0.001$), with the greatest renal impairment in patients receiving high-dose methotrexate-containing protocols. Median hospital stay was 22 days (IQR 14–38) for patients versus 2 days (IQR 1–4) for controls ($p<0.001$), with DDI-associated complications identified as a contributing factor in 17 of 22 prolonged admissions.

3.5 Graphical Summary

Figure 1 illustrates the comparative prevalence of hematological and biochemical complications between the two groups, alongside the distribution of DDI severity across the five major chemotherapy regimens.

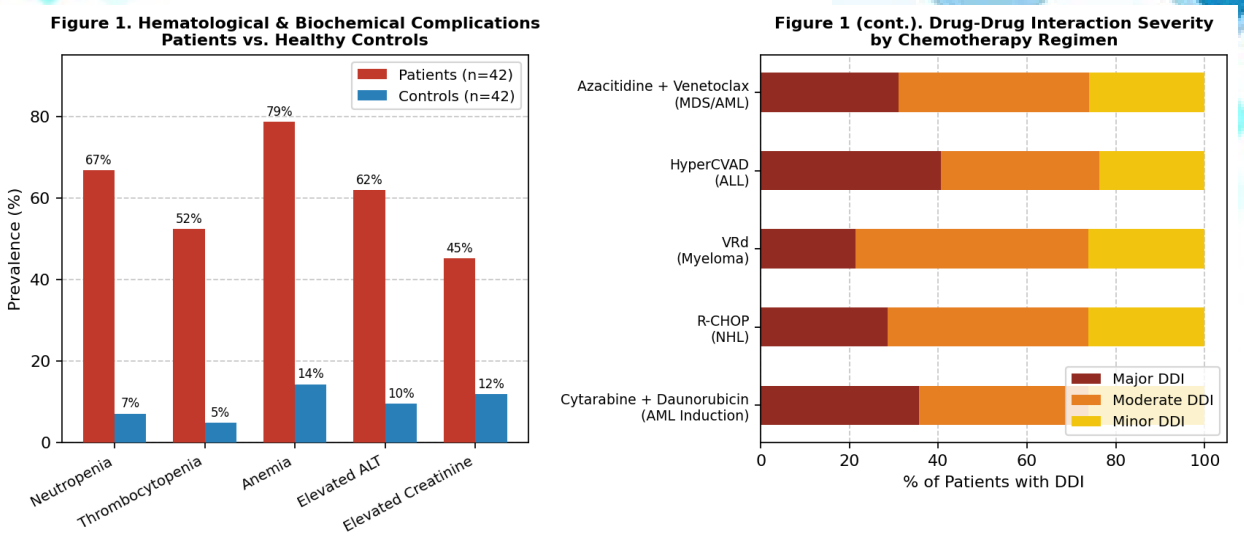

Figure 1. Left panel: Prevalence (%) of hematological and biochemical complications in patients (red) versus healthy controls (blue). Right panel: Distribution of major, moderate, and minor drug-drug interactions by chemotherapy regimen. AML: acute myeloid leukemia; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome.

4. Discussion

The findings of this prospective case-control study underscore the pervasive and clinically consequential nature of DDIs and drug-induced organ toxicity in patients with hematological malignancies receiving multi-drug chemotherapy. The detection of major DDIs in 69.0% of patients — compared with none in matched healthy controls — aligns with and extends findings from prior observational work. Mukherjee et al. reported major DDI rates of approximately 62% in a comparable Iranian cohort of 109 hospitalized hematology patients [40], while Polishchuk et al. observed drug-related problem rates exceeding 70% in a Turkish hematology service [38]. The present study's rigorous case-control design, however, provides the clearest evidence to date that these interactions translate into measurable laboratory abnormalities substantially beyond the baseline expected in a healthy population [33, 34].

The dominance of CYP3A4-mediated interactions in our cohort reflects the central role of this enzyme in metabolizing both cytotoxic agents (vincristine, cyclophosphamide, imatinib) and co-medications (azole antifungals, corticosteroids, proton-pump inhibitors). The voriconazole–vincristine interaction, detected in one-third of our patients, is of particular concern; inhibition of CYP3A4 by voriconazole can increase vincristine exposure two- to fourfold, producing severe constipation, peripheral neuropathy, and syndrome of inappropriate antidiuretic hormone secretion [35, 36]. Guidelines increasingly recommend substituting voriconazole with isavuconazole or posaconazole, which carry lower CYP3A4 inhibitory potential, in vincristine-based regimens [37]. Similarly, the venetoclax–azole interaction mandates venetoclax dose reduction to 10–50 mg daily (from the standard 400 mg) when CYP3A4 inhibitors are unavoidable, yet this adjustment is not consistently implemented in practice [3, 39].

Myelosuppression was overwhelmingly the most prevalent complication in our patient group, consistent with the established biology of cytotoxic chemotherapy. The 78.6% anemia rate and 66.7% grade ≥2 neutropenia rate in our cohort mirror rates reported in the broader literature: Barron et al. documented neutropenia rates of 65–80% across intensive chemotherapy regimens, while the International Society on Thrombosis and Haemostasis has reported thrombocytopenia in 50% of all hematological malignancy patients receiving chemotherapy [35, 36]. The additive myelosuppressive effect of concurrent medications — particularly when azole antifungals elevate cytotoxic drug concentrations — substantially amplifies these rates beyond what would be expected from chemotherapy alone. Nine patients (21.4%) in our cohort developed febrile neutropenia, a complication carrying significant mortality risk and invariably prolonging hospitalization [23].

Hepatotoxicity affected nearly two-thirds of patients (61.9%), a rate strikingly higher than the 9.5% observed in controls. DILI in this context is multifactorial: direct hepatotoxicity from alkylating agents and anthracyclines, CYP enzyme saturation leading to toxic intermediate accumulation, azole-related transaminase elevation, and sinusoidal obstruction syndrome in recipients of high-dose conditioning regimens all contribute [19, 20]. The 2023 update on DILI biomarkers emphasizes that ALT and AST, while widely used, lack specificity and may not correlate with the severity of underlying hepatic injury; emerging biomarkers such as keratin-18, miRNA-122, and glutamate dehydrogenase may offer superior sensitivity [21]. Our data reinforce the need for systematic, protocol-driven hepatic monitoring throughout therapy rather than reactive testing prompted by symptoms.

Nephrotoxicity, present in 45.2% of patients, reflects the complex interplay between nephrotoxic chemotherapeutic agents, co-medications, and the metabolic derangements inherent to hematological malignancies. Methotrexate-related nephrotoxicity is particularly relevant in ALL and NHL regimens; even modest reductions in renal clearance can delay MTX excretion, leading to toxic accumulation [13, 25]. Concurrent use of non-steroidal anti-inflammatory drugs, aminoglycosides, or amphotericin B significantly potentiates this risk. In our cohort, the highest creatinine elevation rates occurred in patients receiving HyperCVAD, consistent with the methotrexate and cytarabine components of this protocol. Routine monitoring of eGFR and urine output during high-risk cycles remains essential, and pharmacist-initiated dose adjustments based on renal function have been shown to reduce toxicity in comparable settings [26, 38].

The substantially prolonged hospital stays observed in the patient group (median 22 vs. 2 days) carry significant economic and quality-of-life implications. DDI-associated complications were identified as contributing factors in the majority of extended admissions, highlighting the downstream systemic burden of unrecognized or

unmanaged interactions. Multidisciplinary pharmacist integration into hematology teams has been demonstrated to reduce DDI-related adverse events by 30–60% in prospective intervention studies [17, 38]. The implementation of real-time clinical decision support systems — embedded within electronic prescribing platforms and calibrated to hematology-specific regimens — represents the most scalable approach to addressing this challenge at the institutional level [12, 24].

Several limitations warrant acknowledgment. The sample size of 42 per group, while adequate for detecting large effect sizes, may underpower detection of less common DDI-outcome associations. The study was conducted at a single tertiary center, potentially limiting generalizability to community hospitals with differing prescribing practices. Additionally, while Micromedex and Lexicomp are validated tools, in silico DDI prediction does not always capture patient-specific pharmacokinetic variability arising from genetic polymorphisms in drug-metabolizing enzymes. Future prospective multi-center studies incorporating pharmacogenomic profiling and longitudinal patient-reported outcome measures would substantially strengthen the evidence base in this area [24, 32].

5. Conclusion

Multi-drug regimens in hematological malignancies impose a substantial and measurable burden of clinically significant drug-drug interactions, severe myelosuppression, hepatotoxicity, and nephrotoxicity that far exceeds the baseline complication rates observed in healthy individuals. With major DDIs affecting nearly seven in ten patients and anemia present in nearly four in five, the pharmacological complexity of modern hematology practice demands a systematic, proactive pharmacovigilance approach. Embedding clinical pharmacists within multidisciplinary hematology teams, deploying CYP-aware electronic prescribing alerts, and instituting mandatory biomarker surveillance at defined cycle intervals are achievable interventions with the potential to reduce preventable toxicity, shorten hospitalization, and preserve the dose intensity that underpins treatment efficacy. As regimens grow more complex — incorporating targeted agents, immunotherapies, and novel small molecules alongside conventional cytotoxics — vigilance against the compounding risks of polypharmacy will only become more essential in safeguarding patient outcomes.

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