

Pharmacokinetic Interactions in Combination Therapies for Acute Myeloid Leukemia

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ABSTRACT

Acute myeloid leukemia is characterized by a malignant proliferation of hematopoietic progenitor cells of the myeloid lineage. The lack of differentiation of precursor cells causes their inability to function normally and the disruption of normal hematopoiesis. This review provides a brief overview of the most important pharmacological strategies that impact on acute myeloid leukemia cure rates and highlights their pharmacokinetic interactions and limitations when used in association. The widespread molecular heterogeneity of acute myeloid leukemia might lead to the identification of “druggable” targets and thus to drugs with an improved therapeutic profile. However, a great deal of focus has to be given to the identification of drug associations with a favourable pharmacokinetic profile that will ultimately contribute to the improved outcomes so cogently needed in acute myeloid leukemia.

Key words: Acute myeloid leukemia; Anthracyclines; Cytarabine; Drug-drug-interactions; FLT3 inhibitors

Abbreviations: **ABCG2**: Breast Cancer Resistance Protein; **AML**: Acute Myeloid Leukemia; **Ara-CTP**: Ara-Cytidine-5'-Triphosphate; **AUC**: Area Under the Curve; **CYP**: Cytochrome P450; **FLT3**: FMS-Like Tyrosine Kinase 3; **LDAC**: Low-Dose Cytarabine; **OCTN**: Organic Cation Transporter

INTRODUCTION

In adults, ~85% of the acute leukemias have a myeloid origin. AML has one of the lowest survival rates of all leukemias [1].

AML is characterized by a malignant proliferation of hematopoietic progenitor cells of the myeloid lineage within the bone marrow. The lack of differentiation of precursor cells causes their inability to function normally and the disruption of normal hematopoiesis with subsequent infection, bleeding, and multi-organ dysfunction [1].

AML has a short median latency period and originates through the induction of mutations affecting critical cancer-related genes [2]. Among those, the most common mutation occurs in the FLT3 gene, involved in the normal proliferation of hematopoietic precursors, and has been observed in approximately one-third of all de novo AML patients and associated with poor prognosis [3]. Epigenetic alterations such as changes in the methylation patterns in leukemia-related genes or their promoter regions have also been reported in therapy-related-AML [4,5].

Outcomes for adult patients with AML have not significantly improved in the past 20 years, mainly due to the hard identification of abnormalities present in AML blasts but not in their normal counterparts. For example, the use of anti-CD123 chimeric antigen receptor T cell therapy in AML patients might need subsequent allogeneic hematopoietic cell transplant because CD123 is found on both AML and normal immature progenitors [6].

Cytarabine and anthracycline-based chemotherapy continues to serve as the foundation for the current standard therapeutic regimen. With such regimens, 60% to 80% of patients > 18 years and <60 years achieve complete remission [7]. For patients older than 60 years with performance status less than 2 and no comorbidities, cytarabine and anthracycline-based chemotherapy is often a plausible option resulting in complete remission rates averaging 50%. Adverse cytogenetics is a strong independent prognostic factor for failure to achieve complete remission. For this subset of older patients, complete remission rates are 30% or less [8].

This review provides a brief overview of the most important pharmacological strategies that impact on AML cure rates and highlights their pharmacokinetic interactions and limitations when used in association. This paper does not cover, however, acute promyelocytic leukemias, which are characterized by peculiar biological and therapeutic aspects.

PHARMACOLOGICAL STRATEGIES FOR AML TREATMENT

Cytarabine is a pyrimidine analogue that utilizes the human equilibrative nucleoside transporter to enter cells. Once inside the cell, cytarabine is phosphorylated to ara-CTP, the

active triphosphate derivative. The anticancer mechanism of cytarabine results from its ability to inhibit DNA polymerase α and β and from the incorporation of ara-CTP into DNA and uracil arabinoside monophosphate into RNA that causes chain termination and subsequent block of DNA synthesis [9]. Ara-CTP competes with deoxycytidine triphosphate for the incorporation into DNA. High cellular concentrations of ara-CTP relative to that of deoxycytidine triphosphate are necessary to favor drug incorporation into DNA and induce leukemic cell death. Accordingly, a low incorporation of ara-CTP in the blasts of patients receiving cytarabine-based therapy is predictive of an adverse outcome [10]. Moreover, cytarabine has been shown to induce apoptosis through the modulation of different signaling events. In particular, it inhibits mitogen-activated kinase, interrupts protein kinase C and downregulates NF- κ B [11].

Anthracyclines form an anthracycline-DNA-topoisomerase II ternary complex and stabilize a reaction intermediate where DNA strands are cut and covalently linked to tyrosine residues of topoisomerase II. This leads to topoisomerase II-mediated DNA damage, growth arrest in G1 and G2, and apoptosis [12]. Some anthracyclines including doxorubicin and idarubicin are also able to inhibit topoisomerase I [13].

A recent advance pertains to the role of proteasome in the anthracycline-induced DNA damage. Doxorubicin diffuses into cancer cells and binds with high affinity to the 20S proteasomal subunit. The complex translocates into the nucleus, where doxorubicin dissociates from the proteasome and binds to DNA [14].

Anthracyclines can generate free radicals through one-electron addition to their quinone moiety, which results in the formation of a semiquinone and reactive oxygen species damaging DNA. Furthermore, following their activation with NAD(P)H oxidoreductases and transition metals, anthracyclines form stable drug-DNA cross-links and less stable drug-DNA adducts. In particular, iron-mediated free radical reactions allow anthracyclines to produce formaldehyde, which conjugates with doxorubicin. The conjugates are able to intercalate into the minor groove of DNA by covalent binding [15].

Finally, changes in telomerase activity and replicative senescence characterized by G0/G1 arrest have been reported after treatment of cancer cells with anthracyclines [16].

Besides cytarabine and anthracycline-based chemotherapy, the progressive identification of an increasing array of cytogenetic and molecular abnormalities characterizing AML is becoming important for the development of appropriate therapeutic approaches. As previously reported, activating mutations in the FLT3 receptor indicates FLT3 as a target for therapy [17]. Given the prevalence and propensity for poor outcome in AML patients harboring FLT3 mutations [18], a variety of FLT3 inhibitors such as sunitinib, sorafenib, midostaurin, and lestaurtinib have entered clinical trials. However, the first-generation of FLT3 inhibitors did not show a sustained FLT3 attenuation in vivo and induced off-target effects [19]. The second-generation inhibitors, represented by quizartinib, demonstrated enhanced FLT3 specificity, were generally well

tolerated, and reached phase III clinical trials [19]. Off-target effects including gastrointestinal upset, reversible QT prolongation and myelosuppression, and resistance to treatment in FLT3-mutated patients have been recorded for quizartinib [20]. Thus, crenolanib has recently emerged as an alternative. Recent studies reported the efficacy of crenolanib in primary blasts resistant to quizartinib [21]. Based on these findings, a single center phase II open label study on crenolanib besylate involving relapsed/refractory AML patients with FLT3 mutations was performed. 34 patients were treated with crenolanib administered at 200 mg/m²/day three times a day continuously in 28 day cycles. Crenolanib was well-tolerated. Its efficacy was recorded on both FLT3 inhibitor-naïve patients and prior FLT3 therapy patients [22].

PHARMACOKINETIC INTERACTIONS AMONG DRUGS USED FOR AML THERAPY

Altered absorption and distribution are the most common and important mechanism responsible for drug interactions in AML patients.

An effective and well-tolerated regimen for the treatment of AML includes the use of cytarabine in association with fludarabine, a purine analogue that modulates the pharmacokinetics of cytarabine. In particular, through potentiating the rate of ara-C accumulation, fludarabine significantly increased the AUC of ara-CTP of 1.8 fold [23]. Clofarabine is a next-generation nucleoside analogue with a better pharmacokinetic and toxicological profile than other deoxynucleoside analogues. In particular, it is characterized by a prolonged retention of its triphosphate derivative in leukemic blasts, and a potent inhibition of DNA synthesis at two critical junctions: DNA polymerase I and RNA reductase [24]. Plasma pharmacokinetic parameters did not show any interaction between cytarabine and clofarabine [25]. Studies of cellular pharmacokinetics performed on 8 AML patients demonstrated that, when administered with cytarabine, clofarabine increased the intracellular concentrations of cytarabine, thus allowing a reduction of the dose or a less intense schedule of administration. However, the effect was recorded in 5 of 8 patients [26]. Taking into account the limited number of patient samples, the study indicates a heterogeneity among patients and a limited efficacy of clofarabine in increasing cytarabine accumulation and efficacy.

High-dose cytarabine is used in the induction treatment of AML patients age 15 to 45 years together with daunorubicin and the topoisomerase poisons etoposide and teniposide [27]. A study explored the modulation of the cellular accumulation of ara-C and its intracellular metabolism in peripheral blast cells from AML patients after preincubation with etoposide or teniposide [28]. The intracellular formation of ara-CTP was reduced after pre-incubation with the topoisomerase poisons. Those results have an important clinical impact and suggest that treatment with etoposide or teniposide should not immediately precede the administration of ara-CTP.

Many preclinical and clinical studies have explored the efficacy of FLT3 inhibitors in association with standard chemotherapy with the aim of achieving their maximum clinical benefit [29-31]. However, the concomitant administration of FLT3 inhibitors with chemotherapy highlighted some pharmacokinetic interactions, some of which may be deleterious to the patient.

α -1-Acid glycoprotein is one of the major drug-binding proteins in humans [32]. In plasma there is an equilibrium between molecules bound to α -1-acid glycoprotein and those free to bind to cellular targets. α -1-Acid glycoprotein is the principle binding protein for some FLT3 inhibitors and anthracyclines [18,33], which can therefore compete or displace each other from α -1-acid glycoprotein binding sites. As an example, α -1-acid glycoprotein can bind lestaurtinib at 1:1 molar ratio [34]. FLT3 inhibitors such as midostaurin or lestaurtinib can displace daunorubicin from α -1-acid glycoprotein, thereby increasing free levels of daunorubicin and resulting in severe toxicity [35]. On the other hand, α -1-acid glycoprotein is an acute phase reactant and its levels can rise following cancer chemotherapy [18]. Since α -1-acid glycoprotein is the main protein binding the FLT3 inhibitor lestaurtinib [36], the concentrations of free lestaurtinib can fluctuate if the drug is administered immediately after chemotherapy.

Another pharmacokinetic interaction deleterious for AML patients resides in the ability of midostaurin to delay the metabolism of daunorubicin, as observed in a pilot trial where midostaurin was used in combination with cytarabine and daunorubicin [18,37]. Furthermore, lestaurtinib is metabolized by CYP34A [38]. Administration of leustartinib with drugs such as anthracyclines that inhibit CYP3A4 [39] may modify the level of the circulating drug and its clinical efficacy.

Some FLT3 inhibitors interact with P-gp and ABCG2. Lestaurtinib and midostaurin inhibit P-gp [40] and pharmacologically relevant concentrations of quizartinib inhibit P-gp and ABCG2 [41]. At 0.1-10 μ M, quizartinib blocked the transport of fluorescent P-gp and ABCG2 substrates in P-gp- and ABCG2-overexpressing cells. At higher concentrations, the drug reduced ABCG2, but not P-gp, ATPase activity. On the whole, those observations could theoretically predict pharmacokinetic interactions between antileukemic drugs that are substrates of P-gp and ABCG2 proteins.

A number of combination therapies are being explored for the treatment of older patients unfit for intensive therapy. Volasertib is a potent cell-cycle kinase inhibitor that blocks cell proliferation through the induction of mitotic arrest and induces apoptosis by targeting Polo-like kinase 1. It is currently under phase-3 investigation in combination with LDAC [42]. The pharmacokinetic profile of volasertib in association with LDAC was similar to that observed for volasertib monotherapy. Moreover, the maximum concentration and AUC values of cytarabine were similar with or without co-administration of volasertib [43].

The combination of barasertib, a selective Aurora B kinase inhibitor, with LDAC did not modify exposure, clearance and distribution at steady state of cytarabine [44].

DISCUSSION

The management of patients with AML can be quite complex. Although hundreds of clinical trials have been completed, the frontline treatment with cytarabine and anthracyclines has remained unchanged for over four decades and long-term survival in AML remains suboptimal.

As the genetic landscape of AML has been mapped and following the success of small-molecule tyrosine kinase inhibitors in chronic myeloid leukemia [45], efforts have been underway to target activated kinases in AML. Activating mutations in FLT3 represent an attractive avenue of molecular targeted therapy for AML. Given the frequency and pathogenetic relevance of FLT3 mutations in AML, FLT3 inhibitors have been explored both as monotherapy and as combination with cytotoxic drugs to improve outcomes. In the therapeutic arena, strategies incorporating FLT3-targeted agents into AML therapy are ongoing, but they have important implications for both chemosensitization and adverse drug interactions. The concomitant administration of FLT3 inhibitors with chemotherapy can actually raise some pharmacokinetic interactions, some of which may be deleterious to the patient. The implications of these findings are clinically important: 1) the cytotoxic drugs to be administered with FLT3 inhibitors should be carefully chosen; 2) when administered in association with cytotoxic drugs, the dose of a drug required to inhibit FLT3 may be completely different from the dose found to inhibit the target in monotherapy and requires adjustments.

Novel compounds with different mechanisms of action are under investigation [42]. They include different nucleoside analogue prodrugs; bortezomib, a proteasome inhibitor; some histone deacetylase inhibitors; tipifarnib, a farnesyltransferase inhibitor; lenalidomide, a thalidomide derivative with immunomodulatory, antiangiogenic, and cytotoxic effects. Some of the above reported drugs have reached phase-2/3 or phase-3 development as monotherapy or in association with cytotoxic chemotherapy [42]. However, unfavourable pharmacokinetic interactions can be predicted for some of those drugs. For example, bortezomib is a CYP3A4 substrate and CYP3A4 inhibitor [46]. Cytarabine, daunorubicin and doxorubicin inhibit CYP3A4. Moreover, doxorubicin and cytarabine are substrates of CYP3A4 [39,47]. Accordingly, cytarabine metabolism was significantly decreased when combined with CYP3A4 inhibitors [48]. Bortezomib may thus inhibit cytarabine and doxorubicin metabolism and this can have important clinical implications.

Tipifarnib has been shown to inhibit in vitro the metabolism of specific CYP3A4, CYP2D6, and CYP2C8/9/10 isoenzymes [49]. These findings indicate a potential interaction with co-administered drugs including cytarabine and anthracyclines that are primarily metabolized by CYP450.

Many studies confirmed that the histone deacetylase inhibitor valproic acid is an inhibitor of CYP450 enzymes and uptake transporters such as OCTN [50,51]. Clinically relevant drug-drug interactions mediated by CYP450 and/or OCTNs can be postulated because some clinically used drugs for AML therapy are CYP450 substrates, as previously reported, and/or OCTN substrates or inhibitors. Reported substrates for OCTN1 include mitoxantrone and doxorubicin [52]. Moreover, through its ability to inhibit histone deacetylase, valproic acid induces expression and activity of human P-gp [53]. The risk of pharmacokinetic drug-drug interactions should be taken into account during concomitant use of valproic acid and CYP and/or OCTN substrates.

Finally, lenalidomide is not a substrate, inhibitor, or inducer of CYP group of enzymes [54]. However, it is a substrate of P-gp [46]. Clinically relevant pharmacokinetic drug-drug interactions are likely to occur between lenalidomide and co-administered P-gp substrates.

On the whole, the massive molecular heterogeneity that characterizes AML might lead to the identification of “druggable” targets and thus to drugs with an improved therapeutic profile. However, a great deal of focus has to be given to the identification of drug associations with a favourable pharmacokinetic profile that will ultimately contribute to the improved outcomes so cogently needed in AML.

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