Available online at www.sciencedirect.com
SCIENCE DIRECT®
Leukemia Research 29 (2005) 263–271
Leukemia Research
www.elsevier.com/locate/leukres

A phase I and pharmacologic study of idarubicin, cytarabine, etoposide, and the multidrug resistance protein (MDR1/Pgp) inhibitor PSC-833 in patients with refractory leukemia

Kenneth S. Bauer[a,b,*], Judith E. Karp[a], Tushar S. Garimella[c], Suhlan Wu[a], Ming Tan[a], Douglas D. Ross[a,d]

[a] *Greenebaum Cancer Center, University of Maryland School of Pharmacy, Allied Health Building Suite 540, 100 Penn Street, Baltimore, MD 21201, USA*
[b] *Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, MD, USA*
[c] *Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore, MD, USA*
[d] *Baltimore Veterans Affairs Medical Center, Baltimore, MD, USA*

Received 18 March 2004; accepted 1 July 2004
Available online 25 September 2004

Abstract

This study was conducted to define the maximum tolerated dose (MTD), dose limiting toxicity (DLT), and pharmacokinetics of idarubicin when administered with and without the P-glycoprotein inhibitor PSC-833 in combination with cytarabine, and etoposide. Fifteen patients with relapsed and refractory acute leukemia were enrolled and received cytarabine as a 7-day continuous infusion, with etoposide and idarubicin administered for any three consecutive days during the cytarabine infusion. Two hours prior to the second dose of idarubicin, PSC-833 administration was initiated. The pharmacokinetics of idarubicin alone and with PSC-833 was assessed at three idarubicin dose levels (6, 8 and 10 mg/m^2). The MTD of idarubicin in this combination was 8 mg/(m^2 day) with a DLT of oral mucositis. The complete remission rate (on an intent-to-treat basis) for this regimen was 33%, with a median duration of 6 months. The clearance of idarubicin was 140 ± 200 and 181 ± 94.3 l/h for idarubicin alone and with PSC-833, respectively. The volume of distribution of the central compartment was 423 ± 443 and 337 ± 394 l for idarubicin alone and in combination with PSC-833, respectively. This combination including PSC-833 was well tolerated. Although a pharmacokinetic interaction might have been expected, PSC-833 did not significantly alter the disposition of idarubicin.

Keywords: P-glycoprotein; Pharmacokinetics; Interaction; Multidrug resistance; Transport proteins

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CR, complete response; PR, partial response; ara-C, cytarabine; MDR1, multidrug resistance; Pgp, P-glycoprotein; SWOG, southwest oncology group; DLT, dose limiting toxicity; MTD, maximum tolerated dose; CML-BC, chronic myelogenous leukemia in blast crisis; MDS, myelodysplastic syndrome; ECOG, eastern clinical oncology group; MUGA, multiple gated acquisition scan; CNS, central nervous system; IRB, institutional review board; ANC, absolute neutrophil count; C_{max}, maximum plasma concentration; AUC, area under plasma concentration curve; AIC, Akaike's information criteria; HPLC, high-performance liquid chromatography

* Corresponding author. Tel.: +1 410 706 3274; fax: +1 410 706 6580.
E-mail address: kbauer@rx.umaryland.edu (K.S. Bauer).

0145-2126/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.leukres.2004.07.002

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous family of hematopoetic malignancies based on different abnormalities and displaying different biologic phenotypes and clinical features. The overall outcomes following chemotherapeutic interventions for AML have not changed substantially for the last 20 years [1,2]. For adults with AML the clinical outcome of treatment is dependent upon a number of variables, including age, pre-existing myelodysplastic syndromes, and chromosomal abnormalities associated with the leukemic clone. Approximately 65–70% of all adults with AML achieve complete remission (CR), roughly 30% of young adults who attain CR achieve long-term disease-free survival. These results have been achieved with the use of the combination of an anthracycline and cytarabine (ara-C) as induction therapy and ara-C based treatment post-remission [3].

While the present complement of cytotoxic agents is effective at inducing complete remissions in the majority of newly diagnosed acute leukemias, many patients relapse and eventually die from drug resistant disease. The drug resistant clone may be present at the time of presentation or alternatively may be acquired later in the course of therapy. The MDR1 gene located on chromosome 7q22 and its encoded 170 kDa P-glycoprotein (Pgp), are expressed at significant levels in diverse hematologic malignancies including AML, and have been considered to contribute to net drug resistance in these diseases. Studies by the southwest oncology group (SWOG) indicate that the MDR-1 gene is expressed with extremely high frequency in elderly AML patients (patients >55 years of age). However, while there is a strong correlation between MDR1 expression and functional drug efflux, the two parameters are not inextricably linked, as functional drug efflux could be detected in a subset of AML populations that did not express MDR-1 and vice versa [4]. This uncoupling of MDR-1 expression and net drug efflux suggests that additional determinants of net intracellular drug metabolism and disposition may influence cellular drug resistance. Nonetheless, Pgp is expressed in a variable percentage of patient leukemic cell samples at diagnosis, and appears to be frequently expressed at relapse. Multiple logs of cells are killed by chemotherapy in patients with AML even when the outcome of treatment is not successful, thus the expression of Pgp even in a small fraction of cells could conceivably be responsible for ultimate treatment failure. It is therefore appropriate to test the use of a drug that can inhibit the function of the MDR drug transporter Pgp as an adjunct to the initial treatment of patients with refractory AML.

Induction therapy for AML is based on the combination of ara-C and an anthracycline. Recently, etoposide has been found to be a highly active agent in de novo relapsed AML and acute lymphoblastic leukemias (ALL) [5]. Idarubicin is a 4-demethoxydaunorubicin derivative that is more lipophilic than and as effective as daunorubicin. However, intracellular idarubicin concentrations do not appear to be as affected to the extent daunorubicin is in cells that express Pgp. The major metabolic byproduct of daunorubicin is daunorubicinol, which does not have an anti-leukemic effect. In contrast, the major metabolite of idarubicin, idarubicinol is not only an active drug, but is a Pgp transportable agent [6] hence, a clinical trial of idarubicin in combination with a Pgp blocker is reasonable.

PSC-833 is a non-immunosuppressive, non-nephrotoxic analogue of cyclosporine-A and is ∼2–10-fold more potent in its ability to inhibit Pgp. This compound is relatively safe by itself, but may potentiate the toxicity of concurrent chemotherapy. Adverse effects observed in healthy volunteers taking PSC-833 alone included dizziness, light headedness, numbness, nausea and bloating. In a phase I study of PSC-833 with etoposide, Boote et al. reported that PSC-833 could be administered with acceptable toxicity. The recommended dose was a continuous infusion of 10 mg/(kg day) over 5 days, with a loading dose of 2 mg/kg given over 2 h [7]. A significant pharmacokinetic interaction was observed when PSC-833 was given in combination with paclitaxel and doxorubicin. The authors of this study reported an 86% increase in doxorubicin exposure, 44% decrease in clearance, and 77% increase in terminal half-life with the addition of PSC-833 [8]. The present study reports a phase I trial of the triple drug combination of ara-C, etoposide and idarubicin in the presence of PSC-833, to determine the dose limiting toxicity (DLT) of this regimen, define the maximum tolerated dose (MTD) of idarubicin while maintaining the doses of the other drugs constant, and characterize the effect of PSC-833 on the pharmacokinetics and disposition of idarubicin.

2. Patients and methods

2.1. Patients

Patients over 18 years of age with established refractory acute leukemia defined as AML primary induction failure, relapsed AML, newly diagnosed high risk AML with poor prognosis (treatment related AML, or AML evolving from myelodysplastic syndromes), chronic myelogenous leukemia in blast crisis (CML-BC), or relapsed acute lymphoblastic leukemia were eligible. Patients with failure of primary induction therapy or who relapsed following CR were eligible if they underwent no more than two prior courses of induction therapy/reinduction therapy (no more than two relapses). Patients' eligibility also included: ECOG performance status 0–2, serum creatinine less than 1.5 mg/dl or creatinine clearance greater than 60 ml/min, serum bilirubin less than 1.5 mg/dl, serum transaminases less than two times the upper limit of normal, and adequate left ventricular function as defined by either echocardiogram or MUGA. Prior chemotherapy (except hydroxyurea or interferon for CML) must have been terminated at least 3 weeks before entering the protocol, and patients had to have recovered from any toxic effects of such treatments. All medications known to increase or decrease cyclosporine-A concentra-