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SHORT COMMUNICATION

The effect of thalidomide on the pharmacokinetics of irinotecan and metabolites in advanced solid tumor patients

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Abstract
Purpose Irinotecan and thalidomide are commonly administered antineoplastic drugs. Combination treatment may potentiate their antitumor effect and protect against irinotecan's intestinal toxicity. We investigated whether thalidomide can modulate the pharmacokinetics of irinotecan and metabolites.
Methods The study employed a crossover design in which advanced solid tumor patients were randomized to two arms and treated with irinotecan 350 mg/m^2 intravenously (IV) every 3 weeks and thalidomide orally (p.o.) 400 mg daily. Pharmacokinetic data when irinotecan was administered as a single agent in each arm were compared to data when the two study agents were co-administered using paired *t* tests. Eighty percent and 90% confidence intervals for the true difference were also calculated.
Results The differences in pharmacokinetic parameters and metabolic markers after thalidomide administration were small and unlikely to be clinically significant. With the exception of APC $T_{1/2}$, none of the upper confidence limits exceeds a 50% increase.
Conclusions This study did not find any clinically meaningful effects of thalidomide on the pharmacokinetics of irinotecan or its metabolites.

Keywords Irinotecan · Thalidomide · Pharmacokinetic interaction · Crossover design

Introduction

Irinotecan has complex pharmacokinetics, and it has been suggested that inhibition of the biliary excretion of SN-38, its active metabolite, may reduce the risk of severe diarrhea [1]. Studies of thalidomide in combination with irinotecan have reported an absence of severe diarrhea when both drugs are combined [2–8]. Mechanistic studies in rats showed that thalidomide can inhibit intestinal production of proinflammatory cytokines and TNF-alpha mRNA expression, leading to reduction of intestinal epithelial apoptosis induced by irinotecan [9]. Thalidomide also inhibited hepatobiliary and intestinal transport of irinotecan, SN-38, and SN-38 glucuronide (SN-38G) in rats [6, 7, 9]. To investigate whether thalidomide had a clinically relevant effect on the pharmacokinetics of irinotecan and metabolites, we conducted a small randomized clinical study with a crossover design in patients with advanced solid tumors.

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Materials and methods

Patient selection

Adult patients (≥18 years of age) with metastatic or unresectable malignancy and for which standard curative or palliative measures do not exist or are no longer effective were included. Eligible patients had a Karnofsky performance status ≥70% and normal organ and marrow function. Patients receiving active therapy for seizures (enzyme-inducing anticonvulsants) were excluded. The study was conducted under a National Cancer Institute (NCI) Investigational New Drug (IND) application for thalidomide. The trial was approved by the Institutional Review Board of the University of Chicago, and patients gave written informed consent prior to study enrollment.

Treatment plan

Irinotecan and thalidomide were supplied by the US National Cancer Institute. Irinotecan was administered IV as a 90-min infusion at a dose of 350 mg/m^2 every 3 weeks. Thalidomide was given orally at 400 mg per day. Patients were randomized to receive therapy on either arm A or arm B. The first 42 days of treatment were considered cycle 1 of arm A, and the first 47 days of treatment (day −6 to day 42) were considered the first cycle of arm B. All patients received irinotecan on days 1 and 22. Patients on arm A received thalidomide on day 15 through day 28. Patients on arm B were treated with thalidomide on day −6 through day 7.

Pharmacokinetic sampling and methods

Patients had blood samples drawn on days 1 and 22 before the start of irinotecan administration and at 0.5, 1, 1.5, 2, 4, 6, 8, 24, 48, and 168 h after the start of infusion. Irinotecan and its metabolites were analyzed as previously described [10].

The area under the plasma concentration–time curve from 0 to 24 h ($AUC_{0-24\,h}$), maximum plasma concentration (C_{max}), and half life ($T_{1/2}$) were estimated by non-compartmental methods using PK Solutions software (version 2.0, Summit Research Services, Montrose, CO). The biliary index (BI), a putative metric for SN-38 AUC in the bile, was calculated as $AUC_{irinotecan} \cdot (AUC_{SN\text{-}38}/AUC_{SN\text{-}38G})$. The relative extent of glucuronidation (GR), a marker for uridine diphosphate glucuronosyltransferase (UGT) activity, was calculated as $AUC_{SN\text{-}38G}/AUC_{SN\text{-}38}$. The relative extent of conversion of irinotecan to SN-38 (REC) and metabolic ratio (MR) were determined as $REC = AUC_{SN\text{-}38}/AUC_{irinotecan}$ and $MR = (AUC_{SN\text{-}38} + AUC_{SN\text{-}38G})/AUC_{irinotecan}$.

Statistical methods

The sample size was chosen to provide sufficient power to detect a 50% increase in the levels of SN-38G when thalidomide is co-administered with irinotecan compared to irinotecan alone, on the assumption that if thalidomide inhibits SN-38's biliary excretion, this should lead to an increased concentration of SN-38's major metabolite, SN-38G. Assuming a coefficient of variation of 30%, a targeted sample size of 12 evaluable patients (6 each in arms A and B) would provide 90% power to detect an effect of this magnitude, using a paired *t* test. For each patient, pharmacokinetic data obtained when irinotecan was being administered as a single agent [day 1 (Arm A) and day 22 (Arm B)] were compared to data when the two study agents were co-administered [day 22 (Arm A) and day 1 (Arm B)]. Pharmacokinetic data from both arms were then pooled for statistical analysis. Confidence intervals (80 and 90%) for the observed difference were also calculated.

Results

Twenty-one patients were enrolled. Due to difficulties in accrual, the trial was terminated after ten of them were evaluable for pharmacokinetics. Reasons for non-evaluability included death, disease progression/relapse during active treatment, and patient withdrawal/refusal after beginning therapy. Pharmacokinetic data from two additional patients were not utilized: one arm B patient did not have blood drawn after day 22 (at 24 and 48 h), and one arm A patient had abnormally high SN-38 concentrations on day 1 ($AUC_{0-24\,h}$ = 1.068 h mg/l). The effect of thalidomide on the pharmacokinetics of irinotecan and metabolites was therefore tested in 8 patients (3 in arm A and 5 in arm B). No statistically significant differences ($P > 0.05$) were observed in pharmacokinetic parameters or metabolic markers when irinotecan was co-administered with thalidomide (Table 1). Due to the small sample size, we also present 80% and 90% confidence intervals. With the exception of APC $T_{1/2}$, none of the upper confidence limits exceeds a 50% increase. (For example, for SN-38G AUC, the upper 90% confidence limit corresponds to a 24% increase.) One of eight patients developed grade 3 diarrhea. Grade 1 or 2 diarrhea was experienced by three patients.

Discussion

The administration of thalidomide with irinotecan had no clinically significant effect on the pharmacokinetics or metabolism of irinotecan in our randomized clinical trial. Two other cancer trials have examined the effects of

Table 1 Pharmacokinetics of irinotecan and metabolites

Pharmacokinetic parameter	−Thalidomide	+Thalidomide	Mean difference (80% CI)	Mean difference (90% CI)	*P*
Irinotecan					
$AUC_{0-24\,h}$ (h mg/l)	27.3 ± 8.6	27.8 ± 11.8	0.5 (−1.7 to 2.7)	0.5 (−2.5 to 3.4)	0.77
$Cmax_{0-24\,h}$ (mg/l)	4.08 ± 0.94	4.38 ± 1.07	0.30 (−0.16 to 0.76)	0.30 (−0.32 to 0.92)	0.38
$T_{1/2}$ (h)	11 ± 3	12 ± 3	1 (−1 to 3)	1 (−2 to 4)	0.46
SN-38					
$AUC_{0-24\,h}$ (h mg/l)	0.333 ± 0.103	0.346 ± 0.159	0.013 (−0.035 to 0.061)	0.013 (−0.051 to 0.077)	0.72
$Cmax_{0-24\,h}$ (mg/l)	0.036 ± 0.015	0.033 ± 0.012	−0.003 (−0.009 to 0.002)	−0.003 (−0.010 to 0.004)	0.45
$T_{1/2}$ (h)	17 ± 11	15 ± 7	−1 (−7 to 4)	−2 (−8 to 6)	0.71
SN-38G					
$AUC_{0-24\,h}$ (h mg/l)	1.02 ± 0.52	1.04 ± 0.78	0.02 (−0.15 to 0.18)	0.02 (−0.20 to 0.24)	0.88
$Cmax_{0-24\,h}$ (mg/l)	0.100 ± 0.059	0.098 ± 0.054	−0.002 (−0.022 to 0.017)	−0.002 (−0.029 to 0.024)	0.87
$T_{1/2}$ (h)	17 ± 10	15 ± 6	−2 (−9 to 5)	−2 (−12 to 7)	0.70
APC					
$AUC_{0-24\,h}$ (h mg/l)	3.01 ± 0.64	2.82 ± 1.16	−0.19 (−0.70 to 0.32)	−0.19 (−0.87 to 0.50)	0.62
$Cmax_{0-24\,h}$ (mg/l)	0.26 ± 0.09	0.22 ± 0.08	−0.03 (−0.08 to 0.01)	−0.03 (−0.09 to 0.03)	0.32
$T_{1/2}$ (h)	8.9 ± 2.3	10.9 ± 6.8	2.0 (−1.6 to 5.6)	2.0 (−2.8 to 6.8)	0.46
$AUC_{0-24\,h}$ ratio					
BI (h mg/l)	9.8 ± 3.7	10.9 ± 6.1	1.1 (−1.2 to 3.4)	1.1 (−2.0 to 4.2)	0.53
GR	3.2 ± 1.6	3.0 ± 1.4	−0.2 (−0.7 to 0.4)	−0.2 (−0.9 to 0.6)	0.70
REC	0.013 ± 0.005	0.014 ± 0.005	0.000 (−0.001 to 0.001)	0.000 (−0.001 to 0.002)	0.64
MR	0.052 ± 0.021	0.051 ± 0.021	−0.001 (−0.005 to 0.003)	−0.001 (−0.007 to 0.004)	0.65

$AUC_{0-24\,h}$ Area under the plasma concentration–time curve from 0 to 24 h, C_{max} maximum plasma concentration, $T_{1/2}$ half life, *SN-38G* SN-38 glucuronide, *BI* biliary index, *GR* glucuronidation ratio, *REC* relative extent of conversion of irinotecan to SN-38, *MR* metabolic ratio

thalidomide on irinotecan's pharmacokinetics, with opposite outcomes. The lack of pharmacokinetic interaction we observed is consistent with results from a study of 17 patients with refractory malignancies. The trial compared pharmacokinetics of irinotecan and metabolites after administration of irinotecan alone (day 1, 125 mg/m^2) and in combination with thalidomide (day 22, 400 mg or 200 mg daily starting on day 3), and concluded there was no drug interaction [11]. This study and our research excluded patients receiving hepatic enzyme-inducing anticonvulsants to avoid an increase in metabolite formation: SN-38G via UGT1A1 [12] and APC via CYP3A4 [13]. A second study of 16 evaluable patients reported increased SN-38 AUC, BI, and REC, and decreased SN-38G AUC and GR during the second drug cycle (no thalidomide) [14]. The different results of the latter study may be due to the nonrandomized design and confounding by co-administered drugs (phenytoin, phenobarbital, and dexamethasone were administered to approximately half the patients). Our study provides further evidence of the lack of a clinically relevant effect of thalidomide on the pharmacokinetics of irinotecan and metabolites and the benefits of randomized clinical trials to test pharmacokinetic questions. Although the number of evaluable patients was small, the confidence limits for the magnitude of change did not suggest a meaningful effect. However, due to the small cohort size, we did not address the potential benefit of thalidomide on the toxicity or efficacy of irinotecan.

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Conflict of interest Drs. Mark J. Ratain and Federico Innocenti receive royalties from the University of Chicago related to *UGT1A1* genotyping.

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