Effects of UGT1A1 genotype on pharmacokinetics and toxicities of belinostat administered by continuous infusion in two clinical trials

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Abstract

Background: Belinostat (BEL), a histone deacetylase inhibitor recently approved for peripheral T-cell lymphoma, is extensively glucurononlated by UGT1A1. Genotypes with reduced UGT1A1 function could lead to higher BEL exposure and toxicities.

Methods: In a Phase I (BPE) and Phase II/B trial (BPAC), 8 400–8 000 mg/m2/24 h was administered as a 48 h continuous infusion in combination with either cisplatin (P) and etoposide (E), or cisplatin (P) and cyclophosphamide (C). In both trials PK of BEL was analyzed and during Cycle 1, clinical outcomes were monitored. Endpoints were associations between UGT1A1 genotype and BEL PK and toxicities.

Results: Overall, PK parameters were not significantly affected by UGT1A1 genotype (P > 0.01) in the BPE trial. Examining doses 400 mg/m2/24 h only, led to increases in AUC (P = 0.003), Cmax (P = 0.003), and decrease in t1/2 (P = 0.003) in pts carrying increasing variants in the combination of UGT1A1*28 and *60. Among all dose levels, incidences of grade 3–4 thrombocytopenia (P = 0.008) and grade 3–4 neutropenia (P = 0.063) were increased in these patients. In the BPAC trial, with 24/26 patients receiving 400 mg/m2/24 h of BEL, associations between genotype and BEL PK and most toxic were insignificant (P > 0.01).

Conclusions: UGT1A1 genotype was associated with increased systemic BEL exposure; increased AUC and increased incidence of toxicities, particularly at doses > 400 mg/m2/24 h. Dose adjustments based on UGT1A1*28 and *60 genotype should be considered to optimize BEL therapy.

Aims

To evaluate the clinical effects of UGT1A1 polymorphisms on:
- BEL-related toxicities: neutropenia, lymphopenia, thrombocytopenia, BEL-related toxicities: neutropenia, lymphopenia, thrombocytopenia, nephropathy, nausea, vomiting and fatigue.

Methods

- 25 patients with cancer receiving BEL (400–8 000 mg/m2/24 h, 48 h continuous infusion) in combination with either cisplatin and etoposide (NCT00100944), or cisplatin, doxorubicin and cyclophosphamide (NCT0100944) were selected for this pharmacokinetic (PK) analysis.
- Patients were genotyped for UGT1A1*1/*28 and UGT1A1*28/28 using fragment analysis or direct sequencing.
- Associations between UGT1A1 polymorphisms and PK parameters of BEL, and the incidence of BEL-related toxicities during cycle 1 were statistically evaluated.

Results

Patient characteristics

- Number of patients: 25 (BPE), 26 (BPAC)
- Gender: Male 15, Female 10
- Age (yr): 54.5 (39.8 – 78.3) 56.3 (23.3 – 76.4)
- Body surface area (m2): 1.70 (1.10 – 1.30) 1.71 (1.24 – 1.69)
- ECOG performance status: 0 1 2
- Race: Caucasian 21 African American 2
- Primary tumor site: Non-small cell lung cancer 3 Adrenocortical cancer 2
- UGT1A1 genotypes: WT/WT 11 60/60 13

PK results

- Dose-normalized AUC (ng h/mg/L)
- Phase I/II trial (BPE): 11.20 (± 0.93) 10.50 (± 1.97)
- Phase II/B trial (BPAC): 0.57 (± 0.03) 0.55 (± 0.03)

Toxicity results

- Grade 3–4 toxicities: neutropenia (P = 0.003), thrombocytopenia (P = 0.003), lymphopenia (P = 0.06)
- Dose: 28 W T/28 H T or 60 W T/60 H T

Conclusions

- Increasing variants in the combination of UGT1A1*28 and *60 were significantly associated with increased BEL AUC at doses > 400 mg/m2/24 h.
- Increasing variants in the combination of UGT1A1*28 and *60 were also associated with a significantly increased incidence of grade 3–4 thrombocytopenia and a trend toward greater incidence of grade 3–4 neutropenia.
- Besides UGT1A1*28, also UGT1A1*60 should be considered for genotype-based dosing of BEL.

Abbreviations

- BEL: Belinostat
- PK: Pharmacokinetics
- UGT1A1: UDP-glucuronosyltransferase 1A1
- ECOG: Eastern Cooperative Oncology Group
- WT: Wild type
- HT: Heterozygous
- WT/WT: Both alleles are WT
- WT/HT: One allele is WT, the other is HT
- HT/HT: Both alleles are HT
- AUC: Area under the concentration-time curve
- CL: Clearance
- Cmax: Maximum concentration
- t1/2: Terminal half-life

Case report

- 62-year-old Caucasian woman diagnosed with NSCLC.
- Medical history: hypercholesterolemia, hypertension.
- Physical exam: BP 147/0 mm Hg, HR 88 bpm, normal EKG (sinus rhythm, QTc: 62.4 ms).
- Neutropenia (grade 3–4) and lymphopenia (grade 3–4) were observed.
- Incidences of grade 3–4 thrombocytopenia and grade 3–4 neutropenia were increased in these patients.

References


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