

## Case Report

# Life-threatening toxicity in a patient with *UGT1A1*\*6 heterozygous polymorphism after irinotecan-based chemotherapy: a case report

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Polymorphism of the *UGT1A1* gene is known to play an important role in irinotecan pharmacokinetics and severe toxicity. A 71-year-old man with lung cancer (squamous cell carcinoma cT2aN3M0 stage IIIB) received irinotecan and cisplatin with concurrent thoracic radiotherapy. Although all treatments were discontinued after day 7, severe leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, and diarrhea developed. His life was at risk, and his ECOG performance status (PS) fell to 4. He had *UGT1A1*\*6 heterozygous and *UGT1A1*\*28 wild-type gene polymorphisms. Considering its frequency in Asians, we should take care when using irinotecan to treat patients with *UGT1A1*\*6 heterozygous polymorphism.

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**Key words:** *UGT1A1*\*6 polymorphism, irinotecan, lung cancer

## Introduction

Irinotecan (CPT-11), a camptothecin analog with potent anticancer activity by the inhibition of topoisomerase I, is applied for a broad spectrum of solid tumors, including colorectal, lung, and gastric cancer [1]. However, it causes side-effects such as severe diarrhea and neutropenia in 20-35% of patients [2]. Irinotecan is metabolized by carboxylesterase to form an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which is subsequently conjugated by UDP-glucuronosyltransferase 1A1 (*UGT1A1*) [3].

Polymorphism of the *UGT1A1* gene is known to play an important role in irinotecan pharmacokinetics and severe toxicity [4]. Here we describe severe toxicity in a patient with *UGT1A1*\*6 genotypes after chemoradiotherapy including irinotecan.

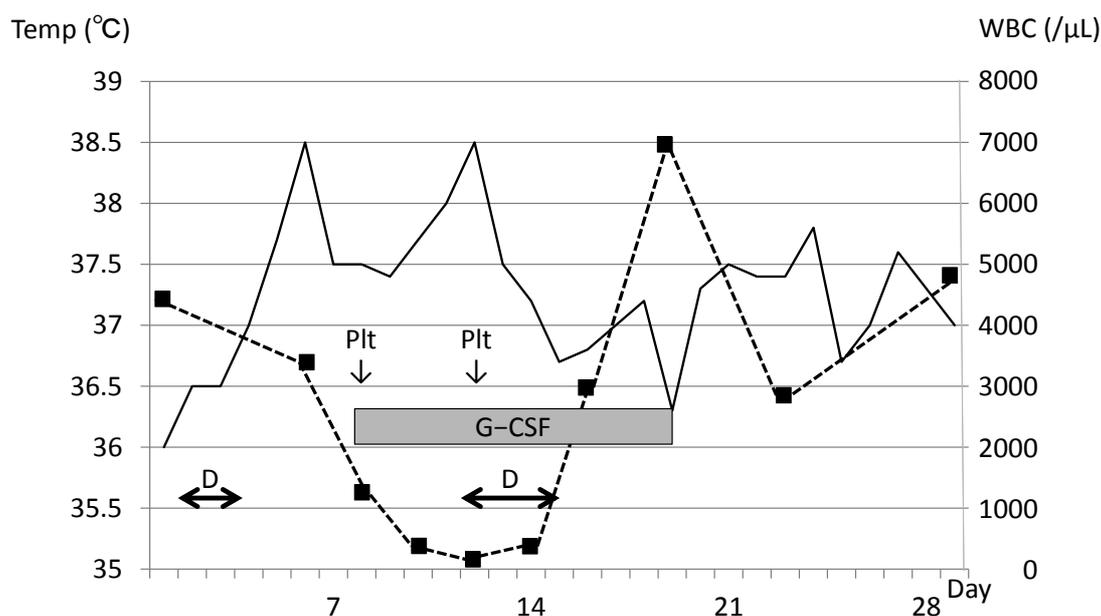
## Clinical summary

The patient was a 71-year-old man with a heavy smoking history, in whom an abnormal shadow was noted on chest images. He was admitted to our hospital for further examination and management of the shadow. Chest radiography and a computed tomography (CT) scan demonstrated a nodule on the right S3 and enlarged mediastinal lymph node. The patient was diagnosed with lung cancer (squamous cell carcinoma cT2aN3M0 stage IIIB) with an ECOG performance status (PS) of 1 based on transbronchial lung biopsy and systemic workups. He received chemotherapy consisting of irinotecan (50mg/m<sup>2</sup> on days 1, 8 and 15) and cisplatin (60mg/m<sup>2</sup> on day 1) with concurrent thoracic radiotherapy, which confirmed feasibility [5]. A chart of his body temperature and white blood cells is shown in Figure 1. Because he had

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**Figure 1.** Chart of body temperature (solid line) and white blood cells (dashed line). D, appearance of diarrhea. Plt, platelet transfusion. G-CSF, daily hypodermic injection of granulocyte colony-stimulating factor.

a high fever and severe toxicity after day 7, all treatments were discontinued. During the first cycle, grade 4 leukopenia, grade 4 neutropenia, grade 3 febrile neutropenia, grade 4 thrombocytopenia, and grade 2 diarrhea developed according to the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE v3.0). Myelotoxicity peaked on day 12 with white blood cells 200/ $\mu\text{L}$ , neutrophils 12/ $\mu\text{L}$ , and platelets 9,000/ $\mu\text{L}$ , respectively. These life-threatening toxicities persisted and PS fell to 4. The patient was treated with granulocyte-colony stimulating factor and cefepime antibiotic, and was given a platelet transfusion. His status resolved on day 19 after intensive care. He then intended to move to another hospital for supportive care. We obtained his consent to perform genetic testing, and he was found to have *UGT1A1*\*6 heterozygous and *UGT1A1*\*28 wild-type gene polymorphisms.

## Discussion

SN-38, an active metabolite of irinotecan, is detoxified by glucuronidation with UGT1A isoforms, 1A1, 1A7, 1A9, and 1A10. Clinical pharmacogenomic studies of irinotecan were conducted in cancer patients. Lyer revealed that patients with the *UGT1A1*\*28 polymorphism had a significantly lower SN-38 glucuronidation rate than those with the normal allele and suffered more severe diarrhea and neutropenia [6].

Innocenti revealed that homozygosity for *UGT1A1*\*28 and total bilirubin levels are strongly associated with severe neutropenia and could be used to identify cancer patients predisposed to the severe toxicity of irinotecan [7]. Therefore, *UGT1A1*\*28 polymorphisms were taken into consideration by the US Food and Drug Administration (FDA) as predictors of irinotecan toxicity in 2005. However, the distribution of polymorphisms shows large interethnic differences. The frequency of *UGT1A1*\*28 is high in Caucasians, whereas it is low in Asians [8].

In Asian studies, *UGT1A1*\*6 allele is associated with low glucuronidation activity and severe toxicity. Minami analyzed Japanese cancer patients treated with irinotecan for association between genetic polymorphisms and toxicities and demonstrated that homozygotes and double heterozygotes of \*6 and \*28 were significantly associated with severe neutropenia [9]. Incidences of grade 3 or 4 neutropenia for patients with wild, heterozygous, and homozygous of *UGT1A1*\*6 or \*28 were 14.3% (3/21), 24.1% (7/29), and 80.0% (4/5) in irinotecan monotherapy and 57.1% (20/35), 70.0% (14/20), and 100% (7/7) in irinotecan with cisplatin therapy, respectively. Han demonstrated homozygosity for *UGT1A1*\*6 was associated with a high risk of severe neutropenia during irinotecan treatment [10]. Incidences of grade 4 neutropenia for patients with wild or heterozygous, and homozygous of *UGT1A1*\*6 were 24% (18/75), and 67% (4/6), respectively. Onoue also demonstrated homozygosity for *UGT1A1*\*6 was

associated with a high risk of severe neutropenia [11]. Incidences of grade 3 or 4 neutropenia for patients with wild, heterozygous, and homozygous of UGT1A1\*6 were 11%(9/70), 35%(17/48), and 50%(3/3), respectively. Although UGT1A1\*6 homozygosity is associated with severe toxicity, its frequency is low. In three papers [12-14], 212 Japanese patients were analyzed for UGT1A1\*28 and \*6. The frequency of \*6/\*6, \*28/\*28 and \*6/\*28 was only 2.8%, 3.3% and 1.9%, respectively, whereas \*6/- was 26.4%. In the present case, a patient heterozygous for UGT1A1\*6 experienced life-threatening toxicity involving neutropenia, thrombocytopenia, febrile neutropenia and diarrhea after irinotecan plus cisplatin chemotherapy. In our prospective phase II study and recent meta-analysis of Asian patients, UGT1A1\*6 polymorphism including homozygotes and heterozygotes was associated with severe neutropenia [15, 16]. Considering the frequency and the present severe case, we should use irinotecan carefully for patients with UGT1A1\*6 heterozygous polymorphism. There might be an additional unknown factor. Regarding efficacy, Han reported an association with UGT1A1 polymorphism that patients with UGT1A1\*6/\*6 had a lower tumor response, and shorter progression-free and overall survival [10]. In the present case, the patient refused to continue chemotherapy or radiotherapy after recovery and transferred to supportive care. Markedly severe toxicity led to decreased therapeutic efficacy.

## References

- Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 352: 476-87, 2005
- Chabot GG, Abigeres D, Catimel G, et al. Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. *Ann Oncol* 6: 141-51, 1995
- Slatter JG, Su P, Sams JP, et al. Bioactivation of the anticancer agent CPT-11 to SN-38 by human hepatic microsomal carboxylesterases and the in vitro assessment of potential drug interactions. *Drug Metab Dispos* 25: 1157-64, 1997
- de Forni M, Bugat R, Chabot GG, et al. Phase I and pharmacokinetic study of the, camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. *Cancer Res* 54: 4347-54, 1994
- Fukuda M, Soda H, Fukuda M, et al. Irinotecan and cisplatin with concurrent split-course radiotherapy in locally advanced nonsmall-cell lung cancer. A multiinstitutional phase 2 study. *Cancer* 110: 606-13, 2007
- Lyer L, Das S, Janisch L, et al. UGT1A1\*28 polymorphism as a determinant of irinotecan disposition and toxicity. *Pharmacogenomics J* 2: 43-7, 2002
- Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 22: 1382-8, 2004
- Ando Y, Chiba M, Nakayama K, et al. The UGT1A1\*28 allele is relatively rare in a Japanese population. *Pharmacogenetics* 8: 357-60, 1998
- Minami H, Sai K, Saeki M, et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A1 genetic polymorphisms in Japanese: roles of UGT1A1\*6 and \*28. *Pharmacogenet Genomics* 17: 497-504, 2007
- Han JY, Lim HS, Shin ES, et al. Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. *J Clin Oncol* 24: 2237-44, 2006
- Onoue M, Terada T, Kobayashi M, et al. UGT1A1\*6 polymorphism is most predictive of severe neutropenia induced by irinotecan in Japanese cancer patients. *Int J Clin Oncol* 14: 136-42, 2009
- Ando Y, Saka H, Ando M, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res* 60: 6921-6, 2000
- Araki K, Fujita K, Ando Y, et al. Pharmacogenetic impact of polymorphisms in the coding region of the UGT1A1 gene on SN-38 glucuronidation in Japanese patients with cancer. *Cancer Sci* 97: 1255-9, 2006
- Sai K, Saito Y, Sakamoto H, et al. Importance of UDP-glucuronosyltransferase 1A1\*6 for irinotecan toxicities in Japanese cancer patients. *Cancer Lett* 261: 165-71, 2007
- Nakamura Y, Soda H, Oka M, et al. Randomized phase II trial of irinotecan with paclitaxel or gemcitabine for non-small cell lung cancer: association of UGT1A1\*6 and UGT1A1\*27 with severe neutropenia. *J Thorac Oncol* 6: 121-7, 2011
- Han F, Guo C, Yu D, et al. Associations between UGT1A1\*6 or UGT1A1\*6/\*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. *Cancer Chemother Pharmacol* 73: 779-88, 2014