Clinical and Economic Impact of Preemptive UGT1A1*28 Genotyping in Metastatic Breast Cancer Patients Treated with Sacituzumab Govitecan: Real-World Experience

PN: PS1-03-17

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Abstract

Sacituzumab govitecan (SG) delivers SN-38, whose clearance depends on UGT1A1. The UGT1A1*28/*28 genotype reduces enzyme activity and increases the risk of severe toxicity, yet preemptive UGT1A1 testing is not routinely performed. We retrospectively reviewed all metastatic breast cancer patients who started SG at our center between August 2024 and July 2025 (n=15); UGT1A1*28 genotyping (KASP probes, €10.51/patient) was requested at physician discretion in those with grade ≥3 CTCAE toxicities (n=8). Five genotyped patients were UGT1A1*28/*28, two UGT1A1*1/*28, and one UGT1A1*1/*1; all experienced at least one grade ≥3 hematologic and/or gastrointestinal event, and three UGT1A1*28 carriers required hospitalization. Mean toxicity-related cost was ≈€8.4K per UGT1A1*28 carrier versus €0 for the UGT1A1*1/*1 patient, whereas preemptively genotyping all 15 patients would have cost €157.65. UGT1A1*28 carriage, particularly UGT1A1*28/*28, was therefore associated with substantial SG-related toxicity and healthcare costs, supporting consideration of preemptive testing for risk stratification.

Introduction

Sacituzumab govitecan (SG) is a Trop-2–directed antibody–drug conjugate that delivers SN-38, the active metabolite of irinotecan. SN-38 is primarily detoxified by the uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) enzyme, and the UGT1A1*28/*28 genotype is associated with reduced enzyme activity and an increased risk of severe neutropenia and diarrhea with SN-38–containing regimens. Although pharmacogenetic guidelines recommend genotype-guided irinotecan dose reductions in UGT1A1*28 poor metabolizers, no validated genotype-based dosing strategy currently exists for SG, and routine UGT1A1 testing is not recommended. Building on emerging data linking UGT1A1*28 homozygosity with higher SG-related toxicity, we explored the clinical and economic implications of a preemptive genotyping strategy in our SG-treated metastatic breast cancer population.

Methods and Materials

We conducted a retrospective observational study of all patients with metastatic breast cancer who initiated sacituzumab govitecan at our tertiary center between August 2024 and July 2025 (n=15). UGT1A1*28 genotyping (KASP probes; unit cost €10.51, including DNA extraction and laboratory procedures) was not systematic but was requested at the treating physician discretion for patients who developed grade ≥3 CTCAE v5.0 toxicities (n=8). From electronic medical records we collected baseline characteristics, toxicity, hospitalizations, resource use, and costs using Andalusian Health Service tariffs (May 2024); primary outcomes were severe toxicity, hospitalization rates, and costs by genotype, and secondary outcomes included dose modifications, G-CSF use, and clinical activity (RECIST 1.1 response and progression-free survival).

Results

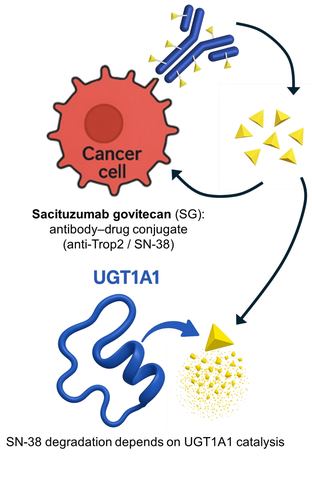
Genotyping and toxicity: Eight of 15 SG-treated patients (53.3%) underwent UGT1A1 testing after developing grade ≥3 toxicity. Among genotyped patients, 5 (62.5%) were UGT1A1*28/*28, 2 (25%) UGT1A1*1/*28, and 1 (12.5%) UGT1A1*1/*1.

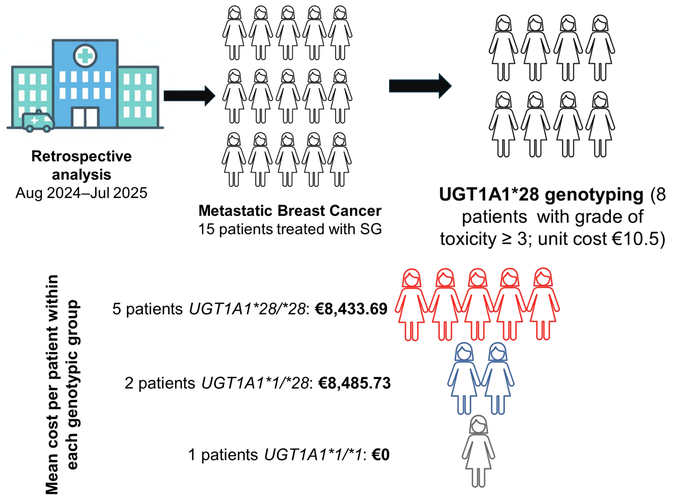
Hospitalizations and costs: Three UGT1A1*28 carriers (37.5%) required hospitalization: one UGT1A1*28/*28 patient was admitted to the ICU for 5 days and to an internal medicine ward for 6 days due to septic shock with grade 4 febrile neutropenia (total cost €14,553.08); one UGT1A1*1/*28 patient was hospitalized for 11 days on the oncology ward for grade 4 febrile neutropenia and gastrointestinal toxicity (€8,485.73); and another UGT1A1*28/*28 patient was hospitalized for 3 days on the oncology ward due to grade 4 neutropenia (€2,314.29). Mean toxicity-related cost per genotyped patient was €8,433.69 for UGT1A1*28/*28 and €8,485.73 for UGT1A1*1/*28, versus €0 for UGT1A1*1/*1, whereas preemptively genotyping all 15 patients would have cost €157.65.

Efficacy and dose modifications: Median progression-free survival among evaluable patients was 6.5 months; two patients remained on treatment without progression at data cut-off. According to RECIST 1.1, we observed 2 partial responses, 4 cases of stable disease, 1 progressive disease, and 1 unevaluable case due to early discontinuation from persistent toxicity in a UGT1A1*28/*28 carrier. All UGT1A1*28/*28 patients required at least one of the following: dose reduction, treatment discontinuation, or G-CSF support; both UGT1A1*1/*28 patients required dose adjustments, whereas neither UGT1A1*1/*1 patient required dose modification.

Discussion

In this small real-world cohort, UGT1A1*28 carrier status, particularly UGT1A128/28, was associated with severe SG-related toxicity, hospitalization, and dose modifications, while antitumor activity appeared similar across genotypes. These results align with the meta-analysis by Dello Russo et al. and the study by Wong et al., both showing higher rates of severe toxicity and treatment modification or discontinuation in UGT1A128/28 patients. Our exploratory cost analysis indicates that the low price of UGT1A128 testing is minimal compared with the substantial costs of managing severe toxicity and prolonged admissions in high-risk patients, although the small sample size, selective genotyping, and absence of formal cost-effectiveness modeling limit firm conclusions.





Conclusions

UGT1A1*28 carrier status, particularly UGT1A1*28/*28 homozygosity, was associated with a higher risk of severe SG-related toxicity, hospitalization, and the need for dose modifications in our real-world metastatic breast cancer cohort. The theoretical cost of preemptive UGT1A128 genotyping for all SG-treated patients (€157.65 for 15 patients) was negligible compared with the toxicity-related costs observed in UGT1A1*28 carriers. These preliminary findings, aligned with external clinical and meta-analytic data, support considering preemptive UGT1A1*28 testing prior to SG initiation to identify high-risk patients who may benefit from closer monitoring, early supportive care, or upfront dose reductions. Prospective studies with larger cohorts and formal pharmacoeconomic analyses are needed before routine genotype-guided SG dosing can be recommended.

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