***Original Article***

# The Relationships between Single Nucleotide Polymorphism and Outcome and Complications of Metastatic Colorectal Cancer Patients who Underwent Irinotecan-based Chemotherapy

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***Key Words***
Metastatic colorectal cancer;
Irinotecan-based chemotherapy;
Single nucleotide polymorphism

***Abbreviations***
SNP: single nucleotide polymorphism;
ALT: alanine aminotransferase;
LLN: lower limit of normal;
ULN: upper limit of normal;
PCR: polymerase chain reaction

***Background.*** Biomarkers for metastatic colorectal cancer may be checked before chemotherapy to achieve the best outcome and to avoid severe adverse effect.
***Material and Methods.*** Medical records from Jan 2004 to Dec 2010 were retrospectively reviewed, and 75 patients who underwent irinotecan-based chemotherapy as first-line chemotherapy for metastaticcolorectal cancer in Taipei Veterans General Hospital were identified. There were twelve-single nucleotide polymorphisms included. Among these patients, survival and adverse events including neutropenia, liver function impairment were analyzed.
***Results.*** There were 75 patients, 48 male (64%) and 27 female (36%). The mean course of irinotecan administered was 9.58. ABCG2 A421C had better overall survival in AC and CC genotype (median survival 23 ± 2.2 month and 26 ± 2.4 month, respectively) compared to those of AA genotype (median survival 8 ± 0.4 month, $p = .002$). TS G12C in 2R/3R was associate with an increased rate of grade 3 neutropenia in GC genotype ($p = .048$). MTHFR C677T was associate with an increased rate of grade 2 elevation of alanine aminotransferase in GC genotype ($p = .044$).
***Conclusion.*** These biomarkers could help to select the better treatment by reducing toxicity associated with irinotecan-based chemotherapy in metastatic colorectal cancer patients, and may improve their survival.
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Colorectal cancer is the most commonly diagnosed malignancy and the third leading cause of cancer death annually in Taiwan.[1] About one fourth of the patients were proved metastasis when diagnosed.

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In patients with stage IV colorectal cancer, irinotecan-based regimen was used widely as first line chemotherapy.[2] Irinotecan inhibits topoisomerase I, which induces transcription errors inhibiting cell proliferation.[3]

Toxicity occurs occasionally during treatment, and there was a significant proportion of patient experiencing severe toxicity, which often leads to dose reductions, delays in treatment administration, and even withdrawal of treatment. Also, toxicity may even lead to death in a rare circumstance.[4,5]

The toxicity related to chemotherapy might be mediated through polymorphisms in metabolism, excretion, or transport genes in a certain degree.[6] And, recent clinical studies suggest that genomic findings can translate into improvements in clinical outcome.[7] Which means, identification of predictive biomarkers for outcome and toxicity to irinotecan-containing treatments could help oncologists to select the best option to avoid severe reactions and to achieve better survival.

Thus, we studied 12 DNA variations in genes which were related to the toxicity of chemotherapy, including 5 fluorouracil (5-FU), oxaliplatin, and irinotecan, to figure out its correlation to adverse events and efficacy of chemotherapy.

## Materials and Methods

### Patient population

We performed a clinical association analysis to investigate twelve single nucleotide polymorphisms (SNP) that might influence the chemosensitivity and adverse effect to irinotecan-based regimen. A total of 75 patients who were diagnosed metastatic colorectal cancerinitially, received surgical intervention for primary tumor, and treated with irinotecan-based regimen as first-line chemotherapy were enrolled between Jan 2004 and Dec 2010 in Taipei Veterans General Hospital. Patients who had undergone concurrent chemoradiotherapy were excluded. This study had been approved by institutional review board of Taipei Veterans General Hospital (IRB No. 2012-06-007A).

Toxic adverse effects, including neutropenia, liver function impairment (elevation of alanine aminotransferase (ALT) or total bilirubin), were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. About neutropenia, grade I was defined as neutrophil count between lower limit of normal (LLN) and 1500/uL, grade II was neutrophil count between 1000/uL and 1500/uL, grade III was neutrophil count between 500/uL and 1000/uL, and grade IV was neutrophil count less than 500/uL. About elevation of ALT, grade I was defined as ALT between upper limit of normal (ULN) and three times of ULN, grade II was between three times of ULN and five times of ULN, grade III was between five times of ULN and twenty times of ULN, and grade IV was ALT more twenty times of ULN. About elevation of total bilirubin, grade I was defined as bilirubin between ULN and 1.5 times of ULN, grade II was between 1.5 times of ULN and three times of ULN, grade III was between three times of ULN and ten times of ULN, and grade IV was bilirubin more thanten times of ULN.

### Genetic analysis

All the SNPs were selected from the HapMap database (data revised in May 2014). The genotypes of these SNPs were shown in supplementary Table 1. When surgical samples collected, the genomic DNA was extracted from normal mucosa and the genotypes were determined by sequencing. Then, DNA was selectively amplified by polymerase chain reaction (PCR) in a DNA thermocycler. A negative control containing no DNA template was included for each of the PCR amplifications. The proper length of the PCR products was checked on a 2.7% agarose gel. The QIAquick PCR purification kit (QIAGEN GmbH, Hilden, Germany) was used to purify the PCR product with agarose gel before being added to the sequencing reaction. The purified PCR products were amplified with BigDye® Terminator cycle sequencing ready reaction mixes (v3.1; Perkin Elmer Applied Biosystems, Foster City, CA) and further analyzed using an automated sequencer (ABI Prism 3100 Genetic Analyzer®; Perkin Elmer Applied Biosystems). Each

**Table 1.** Association between each SNP and adverse events

| | Neutropenia | | | | | Elevation of ALT | | | | | Elevation of total bilirubin | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WNL | Grade I | Grade II | Grade IIII | Grade IV | WNL | Grade I | Grade II | Grade IIII | Grade IV | WNL | Grade I | Grade II | Grade IIII | Grade IV |
| ABCG2-15622A/G | | | | | | | | | | | | | | | |
| AA | 2 | 2 | 1 | 0 | 1 | 2 | 4 | 0 | 0 | 0 | 5 | 1 | 0 | 0 | 0 |
| | (33.3%) | (33.3%) | (16.7%) | | (16.7%) | (33.3%) | (66.7%) | | | | (83.3%) | (16.7%) | | | |
| AG | 10 | 5 | 4 | 8 | 1 | 16 | 6 | 6 | 0 | 0 | 26 | 0 | 1 | 1 | 0 |
| | (35.7%) | (17.9%) | (14.3%) | (28.6%) | (3.6%) | (57.1%) | (21.4%) | (21.4%) | | | (92.9%) | | (3.6%) | (3.6%) | |
| GG | 6 | 4 | 10 | 13 | 8 | 23 | 11 | 4 | 2 | 1 | 35 | 3 | 1 | 1 | 1 |
| | (14.6%) | (9.8%) | (24.4%) | (31.7%) | (19.5%) | (56.1%) | (26.8%) | (9.8%) | (4.9%) | (2.4%) | (85.4%) | (7.3%) | (2.4%) | (2.4%) | (2.4%) |
| ABCG2-15944A/G | | | | | | | | | | | | | | | |
| AG | 2 | 2 | 3 | 8 | 1 | 10 | 5 | 1 | 0 | 0 | 15 | 1 | 0 | 0 | 0 |
| | (12.5%) | (12.5%) | (18.8%) | (50%) | (6.2%) | (62.5%) | (31.2%) | (6.2%) | | | (93.8%) | (6.2%) | | | |
| GG | 16 | 9 | 12 | 13 | 9 | 31 | 16 | 9 | 2 | 1 | 51 | 3 | 2 | 2 | 1 |
| | (27.1%) | (15.3%) | (20.3%) | (22%) | (15.3%) | (52.5%) | (27.1%) | (15.3%) | (2.7%) | (1.3%) | (86.4%) | (5.1%) | (3.4%) | (3.4%) | (1.7%) |
| ABCG2 A421C | | | | | | | | | | | | | | | |
| AA | 1 | 2 | 1 | 0 | 1 | 3 | 1 | 1 | 0 | 0 | 4 | 1 | 0 | 0 | 0 |
| | (20%) | (40%) | (20%) | (%) | (20%) | (60%) | (20%) | (20%) | | | (80%) | (20%) | | | |
| AC | 4 | 4 | 9 | 10 | 4 | 18 | 8 | 3 | 1 | 1 | 27 | 3 | 0 | 0 | 1 |
| | (12.9%) | (12.9%) | (29%) | (32.3%) | (12.9%) | (58.1%) | (25.8%) | (9.7%) | (3.2%) | (3.2%) | (87.1%) | (9.7%) | | | (3.2%) |
| CC | 13 | 5 | 5 | 11 | 5 | 20 | 12 | 6 | 1 | 0 | 35 | 0 | 2 | 2 | 0 |
| | (33.3%) | (12.8%) | (12.8%) | (28.2%) | (12.8%) | (51.3%) | (30.8%) | (15.4%) | (2.6%) | | (89.7%) | | (5.1%) | (5.1%) | |
| MTHFR A1298C | | | | | | | | | | | | | | | |
| AA | 12 | 5 | 10 | 11 | 7 | 23 | 12 | 9 | 0 | 1 | 42 | 1 | 1 | 1 | 0 |
| | (26.7%) | (11.1%) | (22.2%) | (24.4%) | (15.6%) | (51.1%) | (26.7%) | (20%) | | (2.2%) | (93.3%) | (2.2%) | (2.2%) | (2.2%) | |
| AC | 6 | 6 | 5 | 9 | 2 | 18 | 7 | 1 | 2 | 0 | 22 | 3 | 1 | 1 | 1 |
| | (21.4%) | (21.4%) | (17.9%) | (32.1%) | (7.1%) | (64.3%) | (25%) | (3.6%) | (7.1%) | | (78.6%) | (10.7%) | (3.6%) | (3.6%) | (3.6%) |
| CC | 0 | 0 | 0 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | | | | (50%) | (50%) | | (100%) | | | | (100%) | | | | |
| MTHFR C677T | | | | | | | | | | | | | | | |
| TT | 2 | 0 | 2 | 1 | 2 | 2 | 2 | 3 | 0 | 0 | 5 | 1 | 1 | 0 | 0 |
| | (28.6%) | | (28.6%) | (14.3%) | (28.6%) | (28.6%) | (28.6%) | (42.9%) | | | (71.4%) | (14.3%) | (14.3%) | | |
| TC | 8 | 2 | 5 | 8 | 3 | 14 | 6 | 4 | 1 | 1 | 22 | 1 | 1 | 2 | 0 |
| | (30.8%) | (7.7%) | (19.2%) | (30.8%) | (11.5%) | (53.8%) | (23.1%) | (15.4%) | (3.8%) | (3.8%) | (84.6%) | (3.8%) | (3.8%) | (7.7%) | |
| CC | 8 | 9 | 8 | 12 | 5 | 25 | 13 | 3 | 1 | 0 | 39 | 2 | 0 | 0 | 1 |
| | (19%) | (21.4%) | (19%) | (28.6%) | (11.9%) | (59.5%) | (31%) | (7.1%) | (2.4%) | | (92.9%) | (4.8%) | | | (2.4%) |

**Table 1.** Continued

| | Neutropenia | | | | | Elevation of ALT | | | | | Elevation of total bilirubin | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WNL | Grade I | Grade II | Grade IIII | Grade IV | WNL | Grade I | Grade II | Grade IIII | Grade IV | WNL | Grade I | Grade II | Grade IIII | Grade IV |
| UGT1A1-3156G > A | | | | | | | | | | | | | | | |
| AA | 1 (33.3%) | 0 | 0 | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) | 0 | 0 | 2 (66.7%) | 1 (33.3%) | 0 | 0 | 0 |
| AG | 2 (16.7%) | 1 (8.3%) | 2 (16.7%) | 7 (58.3%) | 0 | 4 (33.3%) | 6 (50%) | 1 (8.3%) | 1 (8.3%) | 0 | 11 (91.7%) | 0 | 1 (8.3%) | 0 | 0 |
| GG | 15 (25%) | 10 (16.7%) | 13 (21.7%) | 13 (21.7%) | 9 (15%) | 36 (60%) | 14 (23.3%) | 8 (13.3%) | 1 (1.7%) | 1 (1.7%) | 53 (88.3%) | 3 (5%) | 1 (1.7%) | 2 (3.3%) | 1 (1.7%) |
| TS G12C in 2R/3R | | | | | | | | | | | | | | | |
| CG | 1 (10%) | 0 | 2 (20%) | 5 (50%) | 2 (20%) | 5 (50%) | 3 (30%) | 1 (10%) | 1 (10%) | 0 | 9 (90%) | 0 | 0 | 0 | 1 (10%) |
| GG | 17 (26.2%) | 11 (14.7%) | 13 (20%) | 16 (24.6%) | 8 (12.3%) | 36 (55.4%) | 18 (27.7%) | 9 (13.8%) | 1 (1.5%) | 1 (1.5%) | 57 (87.7%) | 4 (5.3%) | 2 (2.7%) | 2 (2.7%) | 1 (1.3%) |
| ERCC C118T | | | | | | | | | | | | | | | |
| TT | 1 (12.5%) | 3 (37.5%) | 1 (12.5%) | 3 (37.5%) | 0 | 5 (62.5%) | 2 (25%) | 0 | 1 (12.5%) | 0 | 7 (87.5%) | 0 | 1 (12.5%) | 0 | 0 |
| TC | 5 (17.9%) | 4 (14.3%) | 7 (25%) | 8 (28.6%) | 4 (14.3%) | 15 (53.6%) | 8 (28.6%) | 5 (17.9%) | 0 | 0 | 25 (89.3%) | 1 (3.6%) | 0 | 2 (7.1%) | 0 |
| CC | 12 (30.8%) | 4 (10.3%) | 7 (17.9%) | 10 (25.6%) | 6 (15.4%) | 21 (53.8%) | 11 (28.2%) | 5 (12.8%) | 1 (2.6%) | 1 (2.6%) | 34 (87.2%) | 3 (7.7%) | 1 (2.6%) | 0 | 1 (2.6%) |
| XRCC A399G | | | | | | | | | | | | | | | |
| AA | 3 (50%) | 1 (16.7%) | 0 | 1 (16.7%) | 1 (16.7%) | 4 (66.7%) | 1 (16.7%) | 1 (16.7%) | 0 | 0 | 6 (100%) | 0 | 0 | 0 | 0 |
| GA | 8 (29.6%) | 2 (7.4%) | 6 (22.2%) | 10 (37%) | 1 (3.7%) | 18 (66.7%) | 5 (18.5%) | 4 (14.8%) | 0 | 0 | 24 (88.9%) | 2 (7.4%) | 0 | 1 (3.7%) | 0 |
| GG | 7 (16.7%) | 8 (19%) | 9 (21.4%) | 10 (23.8%) | 8 (19%) | 19 (45.2%) | 15 (35.7%) | 5 (11.9%) | 2 (4.8%) | 1 (2.4%) | 36 (85.7%) | 2 (4.8%) | 2 (4.8%) | 1 (2.4%) | 1 (2.4%) |
| XRCC C194T | | | | | | | | | | | | | | | |
| TT | 0 | 0 | 1 (25%) | 1 (25%) | 2 (50%) | 4 (100%) | 0 | 0 | 0 | 0 | 4 (100%) | 0 | 0 | 0 | 0 |
| TC | 7 (20.6%) | 8 (23.5%) | 8 (23.5%) | 8 (23.5%) | 3 (8.8%) | 13 (38.2%) | 12 (35.3%) | 7 (20.6%) | 1 (2.9%) | 1 (2.9%) | 30 (88.2%) | 1 (2.9%) | 2 (5.9%) | 1 (2.9%) | 0 |
| CC | 11 (29.7%) | 3 (8.1%) | 6 (16.2%) | 12 (32.4%) | 5 (13.5%) | 24 (64.9%) | 9 (24.3%) | 3 (8.1%) | 1 (2.7%) | 0 | 32 (86.5%) | 3 (8.1%) | 0 | 1 (2.7%) | 1 (2.7%) |

**Table 1.** Continued

| | Neutropenia | | | | | Elevation of ALT | | | | | Elevation of total bilirubin | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WNL | Grade I | Grade II | Grade IIII | Grade IV | WNL | Grade I | Grade II | Grade IIII | Grade IV | WNL | Grade I | Grade II | Grade IIII | Grade IV |
| XRCC A280G | | | | | | | | | | | | | | | |
| AA | 1 (50%) | 0 | 1 (50%) | 0 | 0 | 1 (50%) | 0 | 0 | 1 (50%) | 0 | 1 (50%) | 0 | 0 | 0 | 1 (50%) |
| GA | 6 (33.3%) | 3 (16.7%) | 2 (11.1%) | 4 (22.2%) | 3 (16.7%) | 8 (44.4%) | 6 (33.3%) | 4 (22.2%) | 0 | 0 | 14 (77.8%) | 2 (11.1%) | 0 | 2 (11.1%) | 0 |
| GG | 11 (20%) | 8 (14.5%) | 12 (21.8%) | 17 (30.9%) | 7 (12.7%) | 32 (58.2%) | 15 (27.3%) | 6 (10.9%) | 1 (1.8%) | 1 (1.8%) | 51 (92.7%) | 2 (3.6%) | 2 (3.6%) | 0 | 0 |
| GSTP1 A313G | | | | | | | | | | | | | | | |
| AA | 12 (26.1%) | 5 (10.9%) | 9 (19.6%) | 13 (28.3%) | 7 (15.2%) | 27 (58.7%) | 13 (28.3%) | 5 (10.9%) | 1 (2.2%) | 0 | 43 (93.5%) | 0 | 0 | 2 (4.3%) | 1 (2.2%) |
| GA | 4 (17.4%) | 6 (26.1%) | 5 (21.7%) | 6 (26.1%) | 2 (8.7%) | 12 (52.2%) | 5 (21.7%) | 4 (17.4%) | 1 (4.3%) | 1 (4.3%) | 18 (78.3%) | 4 (17.4%) | 1 (4.3%) | 0 | 0 |
| GG | 2 (33.3%) | 0 | 1 (16.7%) | 2 (33.3%) | 1 (16.7%) | 2 (33.3%) | 3 (50%) | 1 (16.7%) | 0 | 0 | 5 (83.3%) | 0 | 1 (16.7%) | 0 | 0 |

WNL: within normal limit.

sample was sequenced on both the sense and antisense strands.

The second sequencing procedure with new PCR products was done when any variations found.

### Statistical analysis

The primary analyses were specified to compare adverse effect and survival for each polymorphism. Drug response and clinicopathological variables were related to the corresponding genotype in case-control associations by cross-table analysis. Overall survival rates were compared and verified using the Kaplan-Meier method by a log-rank test and Cox's regression model. Statistical significance was defined as $p < 0.05$. All calculations were performed using SPSS software (ver.16, SPSS Inc.)

## Results

### Patients' characteristics

There were 75 patients included in this study, 48 male (64%) and 27 female (36%). The mean course of irinotecan administered was 9.58. The median time of follow up was 24 months.

### Outcome

A complete set of association between each SNP and the overall survival is included. ABCG2 A421C had better overall survival in AC and CC genotype (median survival 23 ± 2.2 month and 26 ± 2.4 month, respectively) compared to those of AA genotype (median survival 8 ± 0.4 month, $p = .002$; Fig. 1). TS G12C in 2R/3R showed a trend of better overall survivalin GG genotype (median survival 24 ± 2.7 month) compared to those of GC genotype (median survival 15 ± 2.4 month, $p = .067$; Fig. 2).

### Adverse effect

A complete set of association between each SNP and adverse events is included and showed on Table 1.

TS G12C in 2R/3R was associate with an increased rate of grade 3 neutropenia in GC genotype ($p$ = .048; Table 2). ABCG2-15622A/G was associated with neutropenia in in GG genotype (grade 3 and grade 4, $p$ = .067 and .084 respectively; Tables 2 and 3).

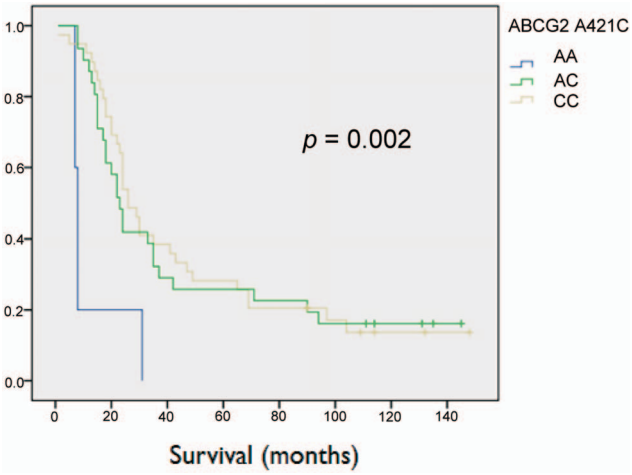


**Fig. 1.** Survival associated with ABCG2 A421C.

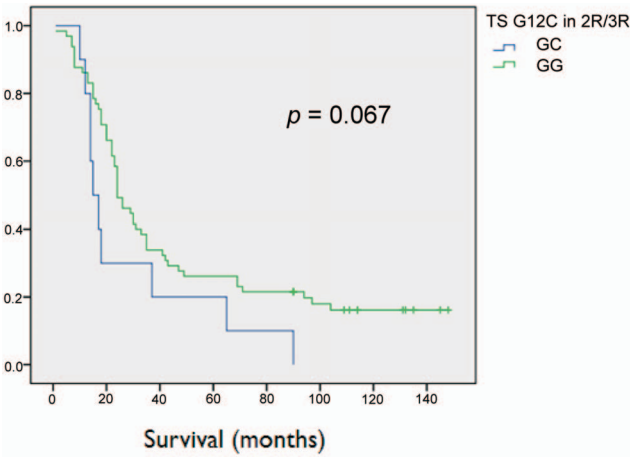


**Fig. 2.** Survival associated with TS G12C in 2R/3R.

**Table 2.** Grade III neutropenia

| | ANC < 1000/uL | ANC > 1000/uL | |
|---|---|---|---|
| ABCG2-15622A/G | | | $p$ = 0.067 |
| GG | 21 (51.2%) | 20 (48.8%) | |
| AA + GA | 10 (29.4%) | 24 (70.6%) | |
| TS G12C in 2R/3R | | | $p$ = 0.048 |
| GC | 7 (70%) | 3 (30%) | |
| GG | 24 (36.9%) | 71 (63.1%) | |

ANC: absolute neutrophil count.

MTHFR C677T was associate with an increased rate of grade 2 elevation of alanine aminotransferase in GC genotype ($p$ = .044; Table 5). UGT1A1-3156G > A showed a trend of grade 1 elevation of alanine aminotransferase in AA + GA genotype ($p$ = .064; Table 4).

## Discussion

To avoid chemotherapy related toxicity and to adjust dose in metastatic colorectal cancer patients treated with irinotecan-based regimen, we analyze 12 polymorphisms through adverse events and treatment outcome.

Thymidylate synthase (TS) plays a role in 5-FU based chemotherapy. TScatalyzes the reductive methylation ofdeoxyuridylate (dUMP) to thymidylate (dTMP). TS blocking results depletion of dTMP levels, and may lead to thymineless death.[8] In our study, TS G12C in 2R/3R has a trend of better survival in GG

**Table 3.** Grade IV neutropenia

| | ANC < 500/uL | ANC > 500/uL | |
|---|---|---|---|
| ABCG2-15622A/G | | | $p$ = 0.084 |
| GG | 8 (19.5%) | 33 (80.5%) | |
| AA + GA | 2 (5.9%) | 32 (94.1%) | |

ANC: absolute neutrophil count.

**Table 4.** Grade I increased ALT

| | ALT > ULN | ALT < ULN | |
|---|---|---|---|
| UGT1A1-3156G > A | | | $p$ = 0.064 |
| GG | 24 (40.0%) | 36 (60.0%) | |
| AA + GA | 10 (66.7%) | 5 (33.3%) | |

ULN: upper limit of normal.

**Table 5.** Grade II increased ALT

| | ALT > 3.0 × ULN | ALT < 3.0 × ULN | |
|---|---|---|---|
| MTHFR C677T | | | $p$ = 0.062 |
| TT | 3 (42.9%) | 4 (57.1%) | |
| TC | 6 (23.1%) | 20 (76.9%) | |
| CC | 4 (9.5%) | 38 (90.5%) | |
| MTHFR C677T | | | $p$ = 0.044 |
| TT + TC | 9 (27.3%) | 24 (72.7%) | |
| CC | 38 (9.5%) | 38 (90.5%) | |

ULN: upper limit of normal.

genotype, and a significance of grade III neutropenia in GC genotype.

The major influence of TS gene is correlated to 5-FU based chemotherapy and there was suggestion to individualize of treatment for patients with colorectal cancer requiring 5-FU based chemotherapy.[9]

Irinotecan is converted into its active form SN38 by carboxylesterases. Like other camptothecin derivatives, SN38 exerts its cytotoxic activity through the inhibition of topoisomerase I. Human topoisomerase I acts in replication and transcription and causing single strand breaks in DNA.[11,12] ABCG2 is a member of the ATP-binding cassette (ABC) transporter. The overexpression of ABCG2 causes decreased accumulation of SN38 and mitoxantrone, and leads to enhance drug efflux from resistant cells.[13]

In our study, ABCG2 A421C showed a significant better survival in AA and AC genotype. ABCG2-15622A/G showed a trend of both grade III and IV neutropenia in GG genotype.

UGT1A1 catalyzes the glucuronidation of SN-38 to inactive SN-38G. A polymorphism consisting on a dinucleotide repeat TA in the promoter region, affecting transcription levels, and a G > A single nucleotide polymorphism in -3156 position of UTG1A1 gene have both been related to toxicity in patients treated with irinotecan.[14,15] In our study, UGT1A1-3156G > A showed the possibility of increased ALT in GG genotype.

This study focused on gene variants from published associations with adverse effect or treatment outcome. Just as we thought, most of the previous results were not shown in this study. The reasons might be issues of multiple comparisons, nonrepresentative patient samples, masked of the subtle variations in patient management when incorporation, or the absence of a validation cohort.[7] Thus, further multi-center randomized trial might be helpful for evaluation the relations between SNPs and outcome and complications and to choose the best regimen individually.

## Conclusion

These biomarkers could help to select the better treatment by reducing toxicity associated with irinotecan-based chemotherapy in metastatic colorectal cancer patients, and may improve their survival.

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# Supplement

**Supplementary Table 1.** Single-nucleotide polymorphisms

| SNP | Genotype |
|---|---|
| ABCG2-15622A/G | AA/AG/GG |
| ABCG2-15944A/G | AA/AG/GG |
| ABCG2 A421C | AA/AC/CC |
| MTHFR A1298C | AA/AC/CC |
| MTHFR C677T | TT/TC/CC |
| UGT1A1-3156G > A | AA/AG/GG |
| TS G12C in 2R/3R | CC/CG/GG |
| ERCC C118T | TT/TC/CC |
| XRCC A399G | AA/AG/GG |
| XRCC C194T | TT/TC/CC |
| XRCC A280G | AA/AG/GG |
| GSTP1 A313G | AA/AG/GG |

SNP: single-nucleotide polymorphism.

**原　著**

# 在接受含 Irrinotecan 化療處方之轉移性大腸直腸癌病人中，單核苷酸多態性與預後及併發症之關聯性探討

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**目的**　於轉移性大腸癌病人接受化療之前，是否可以其單核苷酸多態性來分析其可能預後及嚴重併發症。

**方法**　自 2004 至 2010 年間，統計台北榮民總醫院共有 75 位病患，接受 Irrinotecan 化療處方做為轉移性大腸癌的第一線治療，比較這些患者的 12 種單核苷酸多態性，此篇文章針對這 75 位病患的預後及嚴重併發症進行回顧性研究分析。

**結果**　75 位病患，有 48 位男性及 27 位女性。平均使用 irinotecan 治療的次數為 9.58 次。對比 AA 基因型，ABCG2 A421C 在 AC 及 CC 基因型有較佳存活率 ($p$ = .002)。TS G12C in 2R/3R 在 GC 基因型有較高機率造成第三級以上的嗜中性白血球低下 ($p$ = .048)。MTHFR C677T 在 GC 基因型有較高機率造成第二級以上的丙氨酸轉胺酶升高 ($p$ = .044)。

**結論**　研究特定的單核苷酸多態性，可以幫助我們在治療以 irinotecan 做為轉移性大腸癌的化療病人，得到更好的預後以及避免嚴重併發症的發生。

**關鍵詞**　轉移性大腸癌、Irinotecan 化療、單核苷酸多態性。