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Research Article

Genetic Predictors of Resistance and Survival in Oxaliplatin-Treated Iraqi Patients with Colorectal Cancer

Rehab Abd Almuttaleb Mohammed Jawad[1]*, Bahir Abdul Razzaq Mshimesh[2], Qasim Sharhan Haraj Al-Mayah[3], Fawaz Saad Al-Alloosh[4]

[1]KIMADIA, Ministry of Health, Baghdad, Iraq; [2]Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq; [3]Medical Research Unit, College of Medicine, Al-Nahrain University, Baghdad, Iraq; [4]Department of Medical Oncology, Warith International Cancer Institute, Kerbala, Iraq

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Abstract

Background: Resistance to oxaliplatin-based chemotherapy critically limits treatment efficacy in colorectal cancer (CRC), a leading cause of cancer mortality. While GSTP1 polymorphisms have been studied in other ethnic groups, their impact remains unclear in Middle Eastern populations. ***Objective***: To evaluate the association of GSTP1 rs1695 and rs1138272 polymorphisms with treatment resistance and survival outcomes in Iraqi CRC patients undergoing oxaliplatin-based chemotherapy, considering relevant clinical variables. ***Methods***: A prospective cohort of 120 Iraqi CRC patients was followed for 12 months. Genotyping for GSTP1 variants was performed using PCR and Sanger sequencing. Clinical data, chemotherapy protocols, and survival metrics were collected. Hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) were estimated using Cox regression models. ***Results***: Univariate analysis revealed significant risk factors for progression: liver metastasis (HR=2.19), palliative chemotherapy (HR=1.94), elevated baseline CEA (HR=1.77), and FOLFOX+ bevacizumab treatment (HR=3.78). The GSTP1 rs1695 AG (HR=0.28) and GG (HR=0.18) genotypes showed protective effects. In multivariate analysis, the rs1695 GG genotype independently predicted reduced progression (HR=0.42) and mortality (HR=0.25). FOLFOX-based regimens, especially with bevacizumab, were associated with worse outcomes than XELOX. Grade 2 neurotoxicity correlated with longer PFS. ***Conclusions***: The GSTP1 rs1695 GG genotype is associated with improved survival and reduced progression in oxaliplatin-treated CRC patients, while FOLFOX-based regimens may confer a higher risk. Genotyping GSTP1 may support individualized therapy optimization.

Keywords: Chemotherapy, Colorectal cancer, GSTP1, Oxaliplatin, rs1695, Pharmacogenetics.

التنبؤات الجينية للمقاومة والبقاء على قيد الحياة لدى المرضى العراقيين المصابين بسرطان القولون والمستقيم المعالجين بالأوكساليبلاتين

الخلاصة

الخلفية: مقاومة العلاج الكيميائي القائم على الأوكساليبلاتين تحد بشكل خطير من فعالية العلاج في سرطان القولون والمستقيم (CRC) ، وهو سبب رئيسي للوفيات الناجمة عن السرطان. بينما تمت دراسة تعدد أشكال GSTP1 في مجموعات عرقية أخرى، إلا أن تأثيرها لا يزال غير واضح في سكان الشرق الأوسط. **الهدف**: تقييم ارتباط تعدد أشكال GSTP1 rs1695 و rs1138272 مع مقاومة العلاج ونتائج البقاء على قيد الحياة في مرضى سرطان القولون والمستقيم العراقيين الذين يخضعون للعلاج الكيميائي القائم على الأوكساليبلاتين ، مع الأخذ في الاعتبار المتغيرات السريرية ذات الصلة. **الأساليب**: تمت متابعة مجموعة مستقبلية من 120 مريضا عراقيا بسرطان خلايا القولون والمستقيم لمدة 12 شهرا. تم إجراء التنميط الجيني لمتغيرات GSTP1 باستخدام تسلسل PCR و تسلسل Sanger. تم جمع البيانات السريرية وبروتوكولات العلاج الكيميائي ومقاييس البقاء على قيد الحياة. تم تقدير نسب الخطر (HRs) للبقاء على قيد الحياة بدون تقدم (PFS) والبقاء على قيد الحياة الكلي (OS) باستخدام نماذج انحدار كوكس. **النتائج**: كشف التحليل أحادي المتغير عن عوامل خطر مهمة للتطور: ورم خبيث في الكبد (HR = 2.19) ، والعلاج الكيميائي الملطف (HR = 1.94) ، وارتفاع خط الأساس CEA (HR = 1.77) ، وعلاج FOLFOX + bevacizumab (HR = 3.78). أظهرت الأنماط الجينية GSTP1 rs1695 AG (HR = 0.28) و GG (HR = 0.18) تأثيرات وقائية. في التحليل متعدد المتغيرات ، تنبأ النمط الجيني rs1695 GG بشكل مستقل بانخفاض التقدم (HR = 0.42) والوفيات (HR = 0.25). ارتبطت الأنظمة القائمة على FOLFOX ، خاصة مع bevacizumab ، بنتائج أسوأ من XELOX. ترتبط السمية العصبية من الدرجة 2 ب PFS الأطول. **الاستنتاجات**: يرتبط النمط الجيني GSTP1 rs1695 GG بتحسين البقاء على قيد الحياة وتقليل التقدم في مرضى CRC المعالجين بالأوكساليبلاتين ، في حين أن الأنظمة القائمة على FOLFOX قد تمنح مخاطر أعلى. قد يدعم التنميط الجيني GSTP1 تحسين العلاج الفردي.

* ***Corresponding author***: Rehab A. Mohammed Jawad, KIMADIA, Ministry of Health, Baghdad, Iraq; Email: rehab_abd_almuttalib@uomustansiriyah.edu.iq

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INTRODUCTION

Colorectal cancer (CRC) ranks third globally, with a high mortality rate [1–3]. Oxaliplatin-based doublets such as FOLFOX (5-fluorouracil, oxaliplatin (85 mg/m^2), and leucovorin) and XELOX (capecitabine plus oxaliplatin (130 mg/m^2)) remain first-line standards for advanced CRC, yet intrinsic or acquired resistance limits their therapeutic benefit [4]. The resistance of colorectal cancer cells to oxaliplatin may be evident either immediately or after the initiation of therapy, leading to cancer recurrence or progression

[5]. It is a common finding in empirical studies that carboplatin displays cross-resistance with cisplatin but not with oxaliplatin [6]**.** Glutathione S-transferases (GSTs) may contribute to chemotherapy resistance through several mechanisms. GSTP1, in particular, functions as a facilitator protein within cellular compartments, protecting cells from cytotoxic agents by neutralizing reactive intermediates and facilitating their removal via ATP-dependent transport across biological membranes [7]. Additionally, GSTP1 metabolizes prostaglandins such as PGA2 and PGJ2—compounds known to suppress cellular proliferation and oxidative stress (6). Beyond its detoxification role, GSTP1 modulates key regulatory pathways involved in cell survival and apoptosis. It interacts with critical intracellular signaling molecules, influencing pathways such as JNK1, AKT, and ERK1/2, and suppresses the TRAF2-ASK1-p53 axis, which is essential for DNA damage recognition and apoptosis induction [6,8]. In colorectal cancer, GSTP1 has been shown to upregulate STAT3 expression, thereby promoting tumor cell proliferation, invasion, and metastasis [9]. Understanding the role of GSTP1 gene polymorphisms in mediating resistance to oxaliplatin is therefore of paramount importance for optimizing therapeutic strategies. GSTP1 exerts catalytic (detoxification and drug metabolism), regulatory (apoptosis evasion), and synergistic functions, all of which are implicated in major mechanisms of chemoresistance [10]. The gene encodes glutathione S-transferase Pi, a phase II enzyme that conjugates platinum-based agents with glutathione. Two functional single-nucleotide polymorphisms (SNPs)—rs1695 (A>G; Ile105Val) and rs1138272 (C>T; Ala114Val)—have been shown to affect enzyme activity, potentially modulating both the efficacy and toxicity of oxaliplatin-based chemotherapy. Meta-analyses conducted in European and Asian cohorts have reported conflicting associations between GSTP1 polymorphisms and clinical outcomes in response to oxaliplatin-based chemotherapy; however, comparable data remain lacking for Middle Eastern populations, specifically within Iraq. Given the recognized ethnic variability in allele frequencies, linkage disequilibrium patterns, environmental exposures, and treatment protocols, it is essential to generate local evidence prior to the clinical implementation of pharmacogenetic testing. Therefore, this study aimed to assess the influence of GSTP1 rs1695 and rs1138272 polymorphisms on treatment resistance and survival rate in Iraqi patients diagnosed with advanced colorectal cancer receiving oxaliplatin-based chemotherapy, while additionally examining potential interactions with relevant clinical covariates.

METHODS

Study design and patient selection

A prospective observational cohort study was conducted to assess the impact of GSTP1 polymorphisms on resistance and survival outcomes among Iraqi patients with colorectal cancer treated with oxaliplatin-based chemotherapy. The study enrolled 120 patients between January 2023 and January 2024, with follow-up for a period of 12 months. Participants were recruited from two institutions: the Oncology Teaching Hospital at Medical City, Baghdad, and the Warith International Cancer Institute in Karbala. All patients met the inclusion criteria based on the National Comprehensive Cancer Network (NCCN) guidelines and were evaluated by oncology specialists.

Inclusion criteria

Inclusion criteria required patients to be aged 18 years or older with histologically confirmed CRC, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and no prior exposure to systemic therapy. Adequate hematologic, renal, and hepatic function was verified prior to treatment initiation.

Exclusion criteria

Exclusion criteria included patients with concurrent malignancy or refusal to consent to genetic testing.

Outcome measurements

Demographic and clinical characteristics such as age, sex, tumor stage, metastasis status, chemotherapy protocol, and baseline carcinoembryonic antigen (CEA) levels were recorded. Tumor staging was based on radiological and pathological assessments, with most patients presenting with stage IV disease. Chemotherapy regimens included XELOX, XELOX plus bevacizumab, FOLFOX, and FOLFOX plus bevacizumab. Progression-free survival (PFS) was defined as the interval between chemotherapy initiation and either disease progression or death. Overall survival (OS) was defined as the duration from the start of chemotherapy to death from any cause. Neurotoxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Genotyping

Peripheral blood samples were collected, and genomic DNA was extracted using the ReliaPrep™ Blood gDNA Miniprep kit. Polymerase chain reaction (PCR) was employed to amplify regions containing the target SNPs (rs1695 and rs1138272) using sequence-specific primers. PCR products were visualized via agarose gel electrophoresis [11]. Subsequent genotyping of GSTP1 exon 5 and 6 polymorphisms was performed using Sanger sequencing on the SeqStudio™ Genetic Analyzer System. Sequencing data were analyzed using Mutation Surveyor software to determine genotype distributions [12].

Ethical considerations

The study complied with the principles of Good Clinical Practice (GCP), ethical standards set by the

Research Ethics Committee of Mustansiriyah University of Pharmacy (Certificate no. 37). A statement of consent for publication was obtained from the patient according to the principles of the Declaration of Helsinki. The study maintained strict ethical standards.

Statistical analysis

Genotype frequencies were tested for Hardy–Weinberg equilibrium. Associations between categorical variables were assessed using chi-square or Fisher's exact tests. Survival analyses were conducted using Kaplan–Meier curves and log-rank tests. Cox proportional hazards regression was employed to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for PFS and OS. Variables with $p < 0.10$ in univariate analysis were entered into multivariate models. Statistical significance was set at $p < 0.05$ using SPSS version 26.

RESULTS

In the univariate analysis, several clinical variables were identified as predictors of disease progression (Table 1). Liver metastasis significantly increased the risk of progression (HR = 2.19, $p = 0.004$), whereas other organ involvement was not statistically significant.

Table 1: The hazard ratio for tumor progression

Variables	Patients (n)	HR	95%CI		*p*-value
			Lower	upper	
Age					
< 50	51	ref			
≥ 50	69	1.009	0.623	1.634	0.970
Sex					
Female	59	ref			
Male	61	0.679	0.421	1.095	0.113
ECOG					
0	95	ref			
≥ 1	25	1.118	0.629	1.988	0.703
Stage					
II	7	ref			
III & IV	113	2.771	0.676	11.359	0.157
Organ metastasis					
0	50	ref			
Liver involved	55	0.004	2.192	1.277	3.761
Liver not involved	15	0.492	1.313	0.604	2.856
Chemotherapy settings					
Neoadjuvant	43	ref			
Palliative	64	1.937	1.134	3.308	0.015
Adjuvant	13	0.811	0.302	2.177	0.678
Chemotherapy protocol					
XELOX	46	ref			
XELOX+ bevacizumab	34	1.453	0.806	2.617	0.247
FOLFOX	14	2.027	0.791	5.193	0.141
FOLFOX+ bevacizumab	26	3.783	1.894	7.557	<0.001
Baseline CEA					
< 7	58	ref			
≥ 7	61	0.021	1.771	1.089	2.880
rs1695					
AA	66	ref			
AG	42	0.275	0.143	0.528	<0.001
GG	12	0.181	0.044	0.745	0.018
rs1138272					
CC	91	ref			
CT	27	1.086	0.600	1.966	0.785
TT	2	0.321	0.042	2.448	0.273

(HR) hazard ratio; CI: confidence interval; (ECOG) Eastern Cooperative Oncology Group; (FOLFOX): 5-fluorouracil, oxaliplatin (85 mg/m2) and leucovorin; XELOX: capecitabine plus oxaliplatin (130 mg/m2); (CEA) Carcino Embryonic Antigen.

Palliative chemotherapy was associated with a higher risk of progression compared to neoadjuvant treatment (HR = 1.94, $p = 0.015$). Among chemotherapy protocols, FOLFOX combined with bevacizumab was significantly associated with an increased risk of progression (HR = 3.78, $p < 0.001$). Elevated baseline carcinoembryonic antigen (CEA ≥ 7 ng/ml) also predicted higher progression risk (HR = 1.77, $p = 0.021$). Genotypic analysis revealed that the GSTP1 rs1695 AG and GG genotypes conferred significant protective effects against disease progression compared to the AA genotype (AG: HR = 0.28, $p < 0.001$; GG: HR = 0.18, $p = 0.018$). However, rs1138272 variants (CT and TT) showed no significant impact on progression. For overall survival, univariate Cox analysis indicated that liver metastasis (HR = 2.70, $p = 0.004$), palliative therapy (HR = 2.20, $p = 0.024$), and high CEA levels (HR = 2.07, $p = 0.019$) were significantly associated with increased mortality. FOLFOX and FOLFOX + bevacizumab regimens were linked to worse survival outcomes compared to XELOX (HR = 10.18 and HR = 27.17, respectively; $p < 0.001$ for both). Regarding genetic factors, the rs1695 AG genotype was associated with significantly improved survival (HR = 0.28, $p = 0.002$), while the GG genotype showed a non-significant trend (HR = 0.30, $p = 0.100$) (Table 2). Again, rs1138272 polymorphisms were not

significantly correlated with overall survival. Multivariate Cox regression analysis confirmed that FOLFOX (HR = 2.76, p = 0.043) and FOLFOX + bevacizumab (HR = 4.28, p = 0.001) significantly increased progression risk. Grade 2 neurotoxicity was independently associated with improved progression-free survival (HR = 0.40, p = 0.020). The GG genotype of rs1695 remained an independent predictor of reduced progression (HR = 0.42, p = 0.041) and mortality (HR = 0.25, p = 0.016), while the AG genotype showed a non-significant trend toward benefit (Table 3). These findings indicate that both clinical and genetic factors significantly influence oxaliplatin treatment outcomes in CRC patients.

Table 2: The hazard ratio for overall survival.

Variables	Patients (n)	HR	95%CI		*p*-value
			Lower	upper	
Age					
<50	51	Ref			
≥50	69	0.984	0.547	1.771	0.957
Sex					
Male	59	Ref			
Female	61	0.627	0.353	1.114	0.112
ECOG					
0	95	Ref			
≥ 1	25	1.057	0.524	2.129	0.878
Stage					
II	7	Ref			
III&IV	113	22.647	0.151	3395.871	0.222
Organ metastasis					
0	51	Ref			
Liver involved	55	2.704	1.377	5.312	0.004
Liver not involved	14	1.280	0.445	3.680	0.647
Chemotherapy settings					
Neoadjuvant	43	Ref			
Palliative	64	2.200	1.109	4.365	0.024
Adjuvant	13	0.639	0.173	2.356	0.501
Chemotherapy protocol					
XELOX	46	Ref			
XELOX+ bevacizumab	34	1.381	0.640	2.982	0.411
FOLFOX	14	10.180	3.062	33.839	<0.001
FOLFOX+ bevacizumab	26	27.170	7.524	98.115	<0.001
Baseline CEA	119	2.073	1.128	3.810	0.019
< 7	58	ref			
≥ 7	61	0.019	2.073	1.128	3.810
rs1695					
AA	66	Ref			
AG	42	0.276	0.123	0.617	0.002
GG	12	0.302	0.072	1.257	0.100
rs1138272					
CC	91	Ref			
CT	27	1.128	0.570	2.232	0.729
TT	2	<0.001	<0.001	-	0.979

(HR) hazard ratio; CI: confidence interval; (ECOG) Eastern Cooperative Oncology Group; (FOLFOX): 5-fluorouracil, oxaliplatin (85 mg/m2) and leucovorin; XELOX: capecitabine plus oxaliplatin (130 mg/m2); (CEA) Carcino Embryonic Antigen.

Table 3: Multivariate Analysis for progression-free survival and overall survival

Variables	PFS		OS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Organ metastasis				
Liver involved *vs*. 0	-	-	2.616(0.35-19.73)	0.351
Liver not involved *vs*. 0	-	-	1.459 (156-13.68)	0.741
Chemotherapy settings				
Palliative *vs*. Neoadjuvant	1.133 (0.49-2.60)	0.769	0.579 (0.09-3.95)	0.577
Adjuvant *vs*. Neoadjuvant	0.726 (0.26-2.05)	0.544	0.626 (0.15-2.67)	0.527
Chemotherapy protocol				
XELOX+ bevacizumab vs XELOX	1.273 (0.56-3.92)	0.596	1.068 (0.39-2.93)	0.899
FOLFOX vs XELOX	2.756 (1.03-7.35)	0.043	19.552(4.33-88.30)	<0.001
FOLFOX+ bevacizumab vs XELOX	4.277(1.76-10.38)	0.001	32.47(6.57-160.51)	<0.001
Grade of toxicity 2 *vs*. 1	0.395 (0.18-0.86)	0.020	0.635 (2.7-1.51)	0.305
3 *vs*. 1	0.550 (0.197-1.54)	0.255	0.722 (0.21-2.48)	0.605
CEA ≥ 7 *vs*. < 7	1.378 (0.75-2.54)	0.306	1.196 (0.56-2.55)	0.643
rs1695 GG *vs*. AA	0.422 (0.19-0.96)	0.041	0.252 (0.08-0.77)	0.016
AG *vs*. AA	0.248 (0.05-1.16)	0.076	0.443(0.08-2.36)	0.340

(HR) hazard ratio; CI: confidence interval; (PFS) progression-free survival; (OS) overall survival; (FOLFOX): 5-fluorouracil, oxaliplatin (85 mg/m2) and leucovorin; XELOX: capecitabine plus oxaliplatin (130 mg/m2); (CEA) Carcino Embryonic Antigen.

DISCUSSION

This study presents the first prospective pharmacogenetic analysis of GSTP1 polymorphisms in an Iraqi colorectal cancer population undergoing oxaliplatin-based chemotherapy. The findings reveal that the rs1695 GG genotype confers a notable survival benefit, reducing the risk of progression by

58% and mortality by 75% compared to the AA genotype. These results support the hypothesis that genetic variations affecting GSTP1 enzymatic activity influence therapeutic response. Our analysis also confirms that clinical factors such as liver metastasis, elevated baseline CEA levels, and palliative chemotherapy are strong predictors of poor prognosis. Additionally, treatment with FOLFOX-based protocols, particularly in combination with bevacizumab, was independently associated with worse progression-free and overall survival relative to XELOX regimens. Several hypotheses may explain these findings. First, FOLFOX regimens have been linked to higher rates of severe neutropenia, which can impair treatment continuity and patient quality of life [13]. Second, discrepancies between clinical trial outcomes and real-world data may reflect underlying differences in patient selection, tumor biology, or treatment delivery. Real-world US data (Cancer Care Quality Program) have similarly noted poorer outcomes with FOLFOX, but they do not specify the ethnic demographics of the studied population [14]. Whereas randomized studies report benefit [15,16]. Thus, suggesting the presence of contextual variables. Circadian timing of therapy and sequencing of chemotherapy with antiangiogenic agents such as bevacizumab also appear to impact efficacy, as shown in prior chronotherapy and sequencing studies [17]. Recent studies advocate exploring intermittent treatment schedules and metronomic chemotherapy, aiming to enhance drug exposure and efficacy by normalizing tumor vasculature, minimizing overlapping toxicities, and maximizing antitumor effects [18]. Administering chemotherapy before antiangiogenic agents like bevacizumab has been proposed to optimize drug delivery through vascular normalization [19]. Tailoring treatment schedules to align with individual circadian rhythms represents a promising personalized approach to improving efficacy and tolerability [20,21]. Channeling bias may also contribute; clinicians could preferentially prescribe FOLFOX to patients with greater tumor burden or more aggressive disease not fully captured in recorded variables. Unmeasured molecular characteristics and host pharmacogenetics are likely to further modulate response [13]. Interestingly, Grade 2 neurotoxicity was associated with better outcomes, suggesting that a moderate cumulative exposure to oxaliplatin might reflect effective drug delivery without reaching toxicity-limiting thresholds. This highlights the potential utility of neurotoxicity as a surrogate marker for therapeutic adequacy. The protective effect observed with the GG genotype aligns with the functional consequence of the Val105 variant, which reduces GSTP1 activity and potentially allows for higher intracellular platinum accumulation. The AG genotype showed a trend toward benefit, consistent with a gene-dosage effect.

Study limitations

Limitations of the study include a relatively small sample size, limited duration of follow-up, and the exclusion of other relevant pharmacogenetic markers. Future studies should aim to validate these findings in larger, ethnically diverse cohorts and explore additional genetic determinants of chemotherapy response. Overall, our findings underscore the importance of integrating pharmacogenetic testing into the clinical decision-making process and tailoring chemotherapy protocols based on both genetic and clinical characteristics.

Conclusion

This study identifies the GSTP1 rs1695 GG genotype as a predictive marker of favorable prognosis in Iraqi colorectal cancer patients receiving oxaliplatin-based chemotherapy. In contrast, FOLFOX-based regimens, particularly when combined with bevacizumab, were associated with poorer outcomes relative to XELOX. Incorporating GSTP1 genotyping and optimizing the sequencing and timing of therapeutic regimens could enhance the personalization of chemotherapy in this population.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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