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Original Research

Incidence of oxaliplatin hypersensitivity reaction among colorectal cancer patients: A 5-year retrospective study

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Abstract

Background: Oxaliplatin is a third-generation platinum compound that has efficacy against colorectal cancer. Hypersensitivity reactions during oxaliplatin infusion are a key problem during its use, with the varying incidences and deficiencies of clearly identified risk factors. Objective: To determine the incidence, severity and risk factors of oxaliplatin-related hypersensitivity reaction (HSR). Method: This retrospective study investigated 245 colorectal cancer patients (1,690 treatment cycles) receiving care at King Chulalongkorn Memorial Hospital, Thai Red Cross society between January 1, 2015 and December 31, 2019. The patients' demographic data, laboratory data and clinical features suggesting hypersensitivity reactions to oxaliplatin were reviewed. The Fisher's Exact test and unpaired t-test were used to determine the differences among patients with and without oxaliplatin HSR. The potential risk factors for oxaliplatin HSR were analyzed for statistical significance by logistic regression. Results: A total of 245 colorectal cancer patients (1,690 treatment cycles) were included in this study. The incidence of oxaliplatin HSR was 37.96%, according to the US National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (NTCAE) version 5.0, grade 1, grade 2 and higher grades were 27.35% (67 patients), 6.53% (16 patients) and 4.08% (10 patients), respectively. The proportion of male patients and patients with a history of prior exposure to platinum-based chemotherapy were statistically higher in the HSR group. The eosinophil count and serum creatinine level were also significantly greater in the HSR group. On the contrary, the total lymphocyte count and serum albumin level were significantly lower in the HSR group. The multivariate logistic regression found 5 risk factors with a significant difference. Male gender, prior exposure to platinum-based chemotherapy and elevated eosinophil count were associated with increased risk of oxaliplatin HSR, whereas elevated monocyte count and elevated serum albumin were protective factors for the development of oxaliplatin HSR. Conclusion: Colorectal cancer patients treated with an oxaliplatin-based regimen with male gender, prior exposure to platinum-based chemotherapy and elevated eosinophil count have a greater risk of oxaliplatin related hypersensitivity reactions.

Keywords: Oxaliplatin; Hypersensitivity reactions; Colorectal cancer; Risk factors

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of death due to cancer globally.[1,2] In Thailand, CRC accounts for 11% of cancer burden, which is the only malignancy with an increased incidence in both sexes.[3] CRC treatment is presently a public health priority and comprised of non-pharmacotherapeutic modalities and pharmacotherapy. 5-fluorouracil (5-FU)/leucovorin (LV) or capecitabine are the backbones of the chemotherapeutic regimen, combined with either oxaliplatin (a DNA cross-linker) or irinotecan (a topoisomerase-1 inhibitor). Oxaliplatin-based regimens, such as FOLFOX or CAPEOX, are used more often than irinotecan-based regimen, because of higher efficacy. Consequently, oxaliplatin plus 5-FU/LV or capecitabine, are the mainstreams for both adjuvant and advanced treatments of CRC.[4,5]

Oxaliplatin is a third-generation platinum compound with a 1,2-diaminocyclohexane carrier ligand, has been approved both for treatment of metastatic colorectal cancer and adjuvant treatment in combination with 5-FU and LV or capecitabine.[6] The National Comprehensive Cancer Network (NCCN) guidelines recommended the FOLFOX or CAPEOX as standard regimens for adjuvant chemotherapy for stage II CRC with high-risk factors and stage III CRC as well as the first-line regimen for metastatic CRC.[7,8] The modified FOLFOX regimen, comprises of oxaliplatin 85 mg/m^2 concurrent with LV, 200-400 mg/m^2 on day 1, followed by a bolus 5-FU, 400 mg/m^2, on day 1 and a continuous 5-FU, 1,200 mg/m^2/day, on day 1 and 2 repeated every 2 weeks for 12 cycles. The CAPEOX regimen consists of oxaliplatin, 130 mg/m^2 on day 1 and oral capecitabine 1,000 mg/m^2 twice daily on days 1 to 14 of a 3-week cycle for 8 cycles.[9]

The common adverse reactions of oxaliplatin include nausea, vomiting, diarrhea, and peripheral neuropathy. These adverse reactions can be managed by dosage modification or pre-medication. The serious adverse reactions involve hematologic

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toxicities, presented as neutropenia and thrombocytopenia. Hypersensitivity reaction (HSR) is another serious adverse effect that should be concerned.[10,11] HSR to oxaliplatin has been less frequently described than cisplatin or carboplatin. At the first use, the incidence of HSR to oxaliplatin was very rare, but after the expanded use of oxaliplatin in clinical practice, we are now encountering a significantly increased incidence of oxaliplatin-HSR. Recent reports have shown that the rate of HSR to oxaliplatin has varied from 8.9% to 23.8%.[12-14] HSR to oxaliplatin should be of concern, due to its unpredictability, it is potentially life-threatening requiring the subsequent treatment withdrawal. Yu et al 2021, reported that 85.6% of cancer patients with oxaliplatin-HSR had to interrupt the oxaliplatin course and needed corresponding treatment.[15] Identifying patients with risk of oxaliplatin-HSR is a key clinical issue and several studies have shown supporting risk factors, with various results.[14,16-19] Kim BH et al., 2009 retrospectively analyzed patients receiving oxaliplatin and HSR was associated with younger mean age, female gender and with use of oxaliplatin as salvage therapy.[17] Seki K et al., 2011 reported 5 risk factors associated with oxaliplatin-HSR in CRC patients including female, preexisting allergies, lower level of lactate dehydrogenase (LDH), higher neutrophil count and lower monocyte count.[18] Kim MY et al., 2012 reviewed all patients treated with oxaliplatin and HSR correlated with lower dexamethasone doses.[14] Parel M et al., 2014 identified that developing oxaliplatin-HSR increased with women, younger patients and patients with prior exposure to platinum salts.[19] The aforementioned studies were conducted among patients in the United States, France, South Korea, Japan and China which could be different from Thai patients. In this retrospective study, we explored the incidence, severity and risk factors of oxaliplatin-HSR among Thai patients with CRC.

METHOD

We conducted a retrospective review of the medical records of colorectal cancer patients treated with oxaliplatin-based regimen at King Chulalongkorn Memorial Hospital, Thai Red Cross society, Thailand between January 1, 2015, and December 31, 2019. This study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University (IRB no. 323/61).

All patients received intravenous dexamethasone 8 mg and ondansetron 8 mg as premedication before oxaliplatin infusion. Oxaliplatin-HSR was assessed and classified according to the National Cancer Institute Common Criteria (NCI-CTCAE v5.0)[20] and was noted by attending healthcare staff in the medical records.

Data collection

1) Patient characteristics: gender, age, body surface area (BSA), Eastern Cooperative Oncology Group (ECOG) performance status; scale describing a patient's level of functioning in terms of their ability to care for themselves, daily activity and physical ability[21], medical conditions and preexisting allergies (allergy to specific food or drug). 2) Cancer and chemotherapy characteristics: type of cancer, purpose of treatment, treatment regimen, oxaliplatin dose administration, prior exposure to platinum-based chemotherapy, the number of cycles administered when the episode occurred and the severity of HSR. 3) Baseline laboratory data were obtained for 1 month before the day of administration of oxaliplatin regimen: serum creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), alkaline phosphatase (ALP), serum albumin, white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count and eosinophil count.

In addition, the management, the response to treatment, the mode of prevention used during rechallenging and the final decision (oxaliplatin continuation or withdrawal) were reviewed.

Data analysis

Statistical analysis was performed using the SPSS software, version 22 (IBM Corp., Armonk, NY, USA). After collecting the data, we imputed the missing data by using multiple regression. Quantitative data are reported as means and standard deviation and qualitative data are shown as numbers and percentage. Incidence was defined as the number of cases divided by the total number of patients included in the study. The correlations between HSR to oxaliplatin and several background factors were statistically analyzed using Fisher's exact test or the unpaired t-test. In statistical testing, two-sided p-values ≤ 0.05 were considered statistically significant.

The risk factors examined included gender, age, BSA, ECOG performance status, preexisting allergies and pre-exposure to platinum chemotherapy. The results from laboratory test data were also analyzed. To determine risk factors potentially associated with HSR to oxaliplatin, those factors were collected and subjected to univariate and multivariate logistic regression. All variables with p-values < 0.2 were included in the initial multivariate model. Multivariate analysis with backward stepwise elimination was then conducted to develop the final model. The goodness of fit for each stepwise model was compared with Hosmer and Lemeshow test. A p-value of < 0.05 was considered significant.

RESULTS

Patient characteristics

We retrospectively analyzed the records of 245 colorectal cancer patients (1,690 treatment cycles) who were treated with oxaliplatin-based regimens. The median age was 61 years (range 33-88 years) and 142 (57.96%) were male. Approximately 70% of patients had received capecitabine plus oxaliplatin regimen (CAPEOX). The background characteristics of colorectal cancer patients who had a positive and negative experience of oxaliplatin-HSR and the baseline laboratory data were listed in Table 1.

There were no statistical differences of age, body surface area, dosage regimen, performance status, total infusion course, and history of drug hypersensitivity between the patients without HSR (control group) and with HSR (case group). Compared with women, men had relatively higher susceptibility to HSR

(*p*=0.015). Those patients who had been exposed to platinum compound before this episode of treatment also had higher HSR reports (*p*=0.009). Baseline biochemical examination of blood showed that the percentage of lymphocytes, eosinophils and serum albumin were statistically different between the 2 groups (*p*=0.044, 0.012, 0.024 respectively).

Table 1. Patient characteristics (n=245)

Parameter	Number of patients (%)		p-value
	Patient without HSR (n=152) [Max,Min]	Patient with HSR (n=93) [Max,Min]	
Age (years), mean ± SD	59.34±11.38 [81,33]	59.96±11.19 [88,40]	0.677
Gender: Male/Female	79 (52.0)/73 (48.0)	63 (67.7)/30 (32.3)	0.015*
Body surface area (m^2), mean ± SD	1.62±0.19 [2.23,1.12]	1.64±0.15 [2.01,1.27]	0.370
ECOG Performance Status			
0	1 (0.7)	0 (0.00)	
1	133 (87.5)	79 (84.9)	0.574
2	18 (11.8)	14 (15.1)	
Metastasis, yes	88 (57.9)	46 (49.5)	0.198
Prior exposure to platinum-based chemotherapy, yes	18 (11.8)	23 (24.7)	0.009*
History of drug hypersensitivity, yes	13 (5.3)	12 (4.9)	0.275
Underlying medical condition, yes	97 (63.8)	55 (59.1)	0.499
Regimen			
CAPEOX	104 (68.4)	66 (71.0)	
mFOLFLOX	15 (9.9)	16 (17.2)	0.059
FLOX	33 (21.7)	11 (11.8)	
Purpose			
Adjuvant	81 (53.3)	70 (75.3)	0.001*
Palliative	71 (46.7)	23 (24.7)	
Dose (mg), mean ± SD	177.36±45.78 [250,65]	183.06±37.51 [250,100]	0.290
Dose per body surface area (mg/m^2), mean ± SD	108.71±23.70 [135.80, 43.62]	111.58±21.55 [142.86,55.87]	0.342
Cumulative dose (mg), mean ± SD	1160.53±471.58 [2040,125]	1234.11±465.85 [2400,180]	0.235
Total infusion course, median	8 [12,1]	7 [12,1]	0.844[a]
WBC count ($x10^3/\mu L$)	6.95±2.26 [14.74,2.19]	6.78±2.05 [14.07,3.99]	0.329
Neutrophil count (cells/mm3)	4468.09±1922.92 [12087,1473]	4414.39±1764.801 [11017,1828]	0.827
Total lymphocyte count ($cell/mm^3$)	1690.83±914.56 [6222,131]	1459.30±639.54 [3185,356]	0.033*
Monocyte count ($cell/mm^3$)	479.01±192.56 [995.80,37.98]	444.97±210.39 [1210.02,24.00]	0.196
Eosinophil count ($cell/mm^3$)	142.41±134.24 [716,0]	189.45±170.32 [961,0]	0.017*
Serum albumin (g/dL), n=171	3.76±0.46 [4.5,2] n=98	3.59±0.54 [5,2] n=73	0.024*
Alkaline phosphatase (U/L)	90.89±94.71[869,20]	96.91±98.82 [573,21]	0.635
Serum creatinine (mg/dL)	0.78±0.19 [1.3,0.3]	0.84±0.28 [2.2,0.5]	0.073
- more than 1 mg/dL	14 (9.2)	20 (21.5)	0.007*
eGFR (mL/min)	83.84±27.22 [199.84,26.22]	83.23±26.29 [137.67,15.86]	0.863

*P < 0:05, [a] Mann–Whitney's U-test

mFOLFLOX: Oxaliplatin plus leucovorin and 5-Fluorouracil every 2 weeks

CAPEOX: Intravenous oxaliplatin 130 mg/m^2 (day 1) followed by oral capecitabine 1,000 mg/m^2 twice daily (day 1, evening, to day 15, morning)

WBC white blood cell

FLOX: 5-Fluorouracil plus oxaliplatin on weeks 1,3,5 of 8-week cycle

SGOT: Serum glutamic-oxaloacetic transaminase

SGPT: Serum glutamate-pyruvate transaminase

eGFR: estimated glomerular filtration rate

Incidences of hypersensitivity reaction

During the 5-year follow-up, 93 patients experienced oxaliplatin-HSR. According to NCI-CTCAE v.5, the incidence rate of grade 1, grade 2 and higher grade was 27.3% (67 patients), 6.5% (16 patients) and 4.1% (10 patients), respectively. (Table 2) Oxaliplatin hypersensitivity appeared on a median of 3 infusions (1-11). In addition, out of 23 patients (9.39%) who developed oxaliplatin-HSR at the first and second infusion course, 10 (43.48%) had been exposed to platinum agents before this episode of treatment. The most common HSR were mild cutaneous reactions such as flushing, urticaria, itching and small area erythema, largely on palms and soles. Some patients presented more severe reactions with facial swelling, dyspnea, wheezing, stomach cramp, diarrhea, or changes in blood pressure. (Table 2) Eleven patients were diagnosed with anaphylaxis, with acute and severe symptoms during the infusion or started within 30 minutes after complete infusion. Ten of these were grade 3 HSR, in which the oxaliplatin infusion was immediately discontinued when the reaction occurred and was promptly handled before being admitted into the hospital. (Table 3)

Table 2. Severity and manifestations of oxaliplatin hypersensitivity reactions (n=245)

	Number of patients (%)
Incidence of hypersensitivity	93 (37.96)
Severity	
Grade 1	67 (27.35)
Grade 2	16 (6.53)
Grade 3/4	10 (4.08)
Symptom	
Cutaneous reactions	58 (23.67)
Anaphylaxis	11 (4.49)
Digestive symptoms	20 (8.16)
Respiratory symptoms	17 (6.94)
Blood pressure rising	6 (2.45)
Fever/Chill	4 (1.63)/6 (2.45)
Palpitation	3 (1.22)
Blood pressure lowering	2 (0.82)
Cycle number at event, median (range)	3 (1-11)
Grade 2, median (range)	4 (1-11)
Grade 3, median (range)	2.5 (1-6)

Risk factors for hypersensitivity reaction

To investigate the potential risk factors for the development of oxaliplatin HSR, we applied a logistic regression model, in which the following factors were included: (1) age, (2) gender, (3) metastasis, (4) prior platinum exposure, (5) history of drug hypersensitivity, (6) neutrophil count, (7) lymphocyte count, (8) monocyte count, (9) eosinophil count, (10) serum albumin, (11) serum creatinine, (12) oxaliplatin infusion number and (13) total dose of oxaliplatin. Through the univariate analysis, in total 8 factors had *p*-values < 0.2 which met the criteria for inclusion in multivariate analysis (Table 4).

After the backward stepwise elimination method, 5 final factors were selected: gender, prior platinum exposure, eosinophil count, monocyte count and serum albumin. The odds ratio (95% CI) from the multivariate model was presented in Table 4. We established the incidence of hypersensitivity in colorectal cancer patients treated with this oxaliplatin base regimen(Y) model:

Y=3.419 + [0.966 x (Gender; if male =1)] + [0.818 x (if prior platinum exposure)] + [0.003x(number of eosinophil count in cells/mm^3)] - [0.002x(number of monocyte count in cells/mm^3)] - [1.111x(serum albumin in g/dL)].

DISCUSSION

Hypersensitivity reactions to oxaliplatin result in the withdrawal of the chemotherapy or reducing the number of therapeutic options. The incidence of oxaliplatin HSR is growing as a consequence of the increasing use of oxaliplatin in colorectal cancer. The incidence of oxaliplatin HSR in this study was 37.96%, relatively higher than the rates described in previous studies (8.9% to 23.8%),[12,14,17,22,23] suggesting racial effects and dosage effects. The MOSAIC trial, a large, randomized phase 3 trial in Western countries, showed 10.3% of 1,100 patients who received 5-fluorouracil with oxaliplatin experienced HSR.[23] The report from Japanese patients indicated that 22.9% of 108 patients experienced hypersensitivity.[18] Additionally, the dose of oxaliplatin in the MOSAIC trial was 85 mg per square meter or was reduced to 75 mg per square meter in the event of persistent neuropathy,[23] but the average dose of oxaliplatin in this study was 110 mg per square meter. Interestingly, grade 3/4 HSR in this study was similar to the previous study.[18,23] Ten patients experienced grade 3/4 HSR to oxaliplatin and 6 patients were reintroduced to oxaliplatin. The reintroduction of oxaliplatin was done after skin testing for oxaliplatin sensitivity or using a 12-step desensitization protocol, developed by the Dana–Farber Cancer Institute and the Brigham and Women's Hospital.[24]

The identification of the risk of developing HSR is an important issue for the prevention and related management of serious events. The risk factors to platinum drugs related to HSR, especially carboplatin and cisplatin were examined. Only a few studies were focused to identify potential risk factors for oxaliplatin-related HSR.[25] This study emphasized the risk factors to recognize patients at risk of oxaliplatin-related HSR. Logistic regression analysis found five significant factors, three risk factors (male, prior platinum exposure, eosinophil count) and two protective factors (monocyte count, serum albumin).

Okayama et al., reported that male patients and eosinophil count in peripheral blood were independent variables for oxaliplatin-related HSR,[26] which were similar to our finding. Eosinophil, one of the immunologic cells, absolutely characterizes drug HSR, especially drug eruptions, consequently in patients with high eosinophil counts, this may be a component in mechanisms of HSR to oxaliplatin.[26,27] This is contrary to Parel et al., Seki et

Table 3. Characteristics of the ten patients with grade 3/4 oxaliplatin hypersensitivity

No., Gender, Age (years)	Prior plt exp	Metastasis	Regimen	Purpose	Dose/BSA (mg/m2)	Cycle No. at event	Onset of HSR (minutes)	Total cycle	Treatment	Management
1,F,59	N	N	CAPEOX	A	130	5	50	5	1. CPM 10 mg, Dexamethasone 5 mg IV STAT 2. Hold 30 minutes then slow infusion about 6 hours	Discontinue and adjust to single capecitabine then re-evaluate
2,M,59	N	N	CAPEOX	A	130	2	90	6	1. Discontinue 2. Hyoscine-N-butyl bromide 20 mg IV STAT and hydration	1. Add loperamide 2 mg Sig. 2 caps on CMT day 2. Add CPM 10 mg IV pre CMT 3. Rechallenge with prolonged infusion time (4 hours), finally complete total 6 cycles
3,F,60	Y	N	mFOLFLOX	A	85	2	20	12	1. Hold and reduce rate of administration to 80 mL/hr 2. CPM 10 mg, Dexamethasone 5 mg IV STAT 3. Adrenaline 0.3 mg IM	12 step desensitization protocol, finally complete total 12 cycles
4,F,62	Y	Y	FLOX	P	80	2	120	4	1. Adrenaline 1 mg IM and hydration	1. 12 step desensitization protocol with mild HSR through desensitization. 2. Patient requested to discontinue after the 4th cycle
5,M,47	N	N	mFOLFLOX	A	85	3	110	8	1. Discontinue 2. Dexamethasone 10 mg IV STAT 3. Adrenaline 0.5 mg IM	1. 12 step desensitization protocol, but grade-2 HSR through to the 8th cycle 2. Discontinue after the 8th cycle
6,M,45	Y	N	CAPEOX	A	100	2	15	3	1. Hold 2. Adrenaline 0.3 mcg IM and hydration 3. Admit and rechallenge oxaliplatin 20-40 mL/hr	1. Rechallenge with prolonged infusion time (4 hours), grade 2 HSR occurred so discontinue. 2. Skin test: Positive
7,M,47	Y	N	FLOX	P	85	1	90	6	1. Hold and oxygen therapy 2. Adrenaline 0.5 mg IM and Dexamethasone 10 mg IV 3. Admit and then slow infusion about 4 hours	1. Skin test: Negative 2. rechallenge (2nd cycle) with prolonged infusion time (6 hours), but mild HSR. 2. 12 step desensitization protocol (3rd -6th cycle)
8,M,56	N	N	mFOLFLOX	A	80	6	80	6	1. Hold 2. Symbicort™ (160/4.5) 4 puffs and oxygen therapy 3. CPM 10 mg IV 4. Continue infusion rate 80 mL/hr	Discontinue according to therapeutic plan
9,M,44	N	N	CAPEOX	A	90	6	120	6	1. Hyoscine-N-butyl bromide 20 mg IV and CPM 10 mg IV STAT	Discontinue according to therapeutic plan
10,F,73	Y	Y	CAPEOX	P	120	3	120	3	1. Loperamide 2 mg 2 capsules STAT 2. Hydration	Discontinue [Hand foot syndrome grade 3]

No.=Number
Prior plt exp= Prior platinum exposure
Purpose: A=Adjuvant, P=Palliative
CMT=Chemotherapy
HSR= Hypersensitivity reaction
mFOLFLOX: Oxaliplatin plus leucovorin and 5-Fluorouracil every 2 weeks
CAPEOX: Intravenous oxaliplatin 130 mg/m^2 (day 1) followed by oral capecitabine 1,000 mg/m^2 twice daily (day 1, evening to day 15, morning)

Table 4. Univariate analysis and multivariate analysis for candidate risk factors for oxaliplatin hypersensitivity [N=245]

	Univariate analysis				Multivariate analysis			
Factors	**B**	**Adjusted OR**	**95%CI**	**p-value**	**B**	**Adjusted OR**	**95%CI**	**p-value**
Age	0.005	1.005	0.982-1.028	0.675				
Gender, male	0.663	1.941	1.132-3.326	0.016*	0.966	2.628	1.450-4.763	0.001
Metastasis, yes	-0.034	0.712	0.424-1.196	0.199				
Prior platinum exposure, yes	0.894	2.446	1.238-4.834	0.010*	0.818	2.265	1.079-4.755	0.031
History of drug hypersensitivity, yes	0.460	1.584	0.69-3.637	0.278				
Neutrophil count (cell/mm3)	0.0002	0.99998	0.9998-1.0002	0.826				
Total lymphocyte count (cell/mm^3)	0.0004	0.9996	0.9992-0.9999	0.037*				
Monocyte count (cell/mm^3)	-0.001	0.999	0.998-1.000	0.197	-0.002	0.998	0.996-0.999	0.007
Eosinophil count (cell/mm^3)	0.002	1.002	1.000-1.004	0.020*	0.003	1.003	1.001-1.005	0.004
Serum albumin (g/dL)	-0.787	0.455	0.258-0.804	0.007*	-1.111	0.329	0.170-0.638	0.001
Serum creatinine (mg/dL)	1.128	3.090	0.984-9.707	0.053				
Oxaliplatin infusion number (times)	0.028	1.028	0.929-1.138	0.589				
Total dose of oxaliplatin (mg)	0.0003	1.000	1.000-1.001	0.234				
Constant					3.419			

*p < 0.05

al. and Kim et al., studies which suggested that females were at higher risk of oxaliplatin-related HSR,[17-19] explained by a possible role of hormonal influences. Several studies have also reported no correlation between gender and HSR.[12,28] Our study demonstrated that prior platinum exposure was the independent risk factor that was distinguished from previous studies.

On the other hand, we found that lower monocyte count and serum albumin was significantly associated with the incidence of oxaliplatin-related HSR. Seki et al., also suggested that female, preexisting allergies, lower LDH level, higher neutrophil count and lower monocyte count were associated with the incidence of HSR.[18] Serum albumin is commonly utilized as a marker of nutritional status. Malnutrition degrades both the innate and adaptive immune system.[29] Low serum albumin level increases vascular permeability and increases interstitial volume, which potentiates immediate HSR.[30] However, Nishihara et al., reported that serum albumin level above 4.1 g/dL was the potential risk associated with the incidence of oxaliplatin-related HSR. Oxaliplatin may also act as a hapten: a small molecule which, when combined with a larger carrier such as a protein can elicit the production of antibodies that bind specifically to it, binding to macromolecular carrier proteins, such as albumin.[31] A possible reason for the variation of risk factors was the ethnic differences between the participants in this study. Finally, we found that treatment regimen and oxaliplatin dose were not associated with an increased risk of oxaliplatin-related HSR.

Strength and limitations

This retrospective study was conducted to clarify the risk factors for oxaliplatin-related HSR in Southeast Asia and demonstrated the management of severe oxaliplatin-related HSR in the real situation. Limitations of this study include its retrospective design and incomplete clinical data. Some medical records were insufficient, and hypersensitivity symptoms were not actively followed.

Suggestion

Further prospective studies are needed to refine this oxaliplatin-related hypersensitivity prediction model to be more precise and develop the final model as a guide to prevent oxaliplatin-related HSR. Finally, the caregiver team's vigilance should be improved with males, prior platinum exposure, eosinophil count, monocyte count and serum albumin.

CONCLUSION

Oxaliplatin-related hypersensitivity is a significant potential adverse reaction. The incidence was approximately 38%, with grade 3/4 events in 4% of patients. In this study, males, prior platinum exposure, eosinophil count, monocyte count and serum albumin were the independent risk factors that were associated with the incidence of oxaliplatin-related hypersensitivity.

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CONFLICTS OF INTEREST/COMPETING INTERESTS

The authors declare that there have no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection were performed by Sirinoot Palapinyo. The data analysis was performed by Sirinoot Palapinyo and Nutthada Areepium. The first draft of the manuscript was written by Sirinoot Palapinyo and all authors commented and edited previous versions of the manuscript. All authors read and approved the final manuscript. The content has not been published or submitted for publication elsewhere.

ETHICS APPROVAL

This study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University (IRB no. 323/61).

References

1. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89-103. https://doi.org/10.5114/pg.2018.81072
2. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2. 2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(3):329-59. https://doi.org/10.6004/jnccn.2021.0012
3. Lohsiriwat V, Chaisomboon N, Pattana-Arun J. Current Colorectal Cancer in Thailand. Ann Coloproctol. 2020;36(2):78-82. https://doi.org/10.3393/ac.2020.01.07
4. Huang W-K, Hsu H-C, Chang S-H, et al. Real-World Effectiveness of Adjuvant Oxaliplatin Chemotherapy in Stage III Colon Cancer: A Controlled Interrupted Time Series Analysis. Front Pharmacol. 2021;12:693009. https://doi.org/10.3389/fphar.2021.693009
5. Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol. 2018;29(1):44-70. https://doi.org/10.1093/annonc/mdx738
6. Devanabanda B, Kasi A. Oxaliplatin. In: StatPearls. Treasure Island (FL): StatPearls Publishing LLC.; Dec 28, 2021.
7. Zhao L, Liu R, Zhang Z, et al. Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials. Colorectal dis. 2016;18(8):763-72. https://doi.org/10.1111/codi.13381
8. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN Guidelines Insights: Colon Cancer, Version 2.2018. J Natl Compr Canc Netw. 2018;16(4):359-69. https://doi.org/10.6004/jnccn.2018.0021
9. Jeon H-J, Woo J-H, Lee H-Y, et al. Adjuvant Chemotherapy Using the FOLFOX Regimen in Colon Cancer. J Korean Soc Coloproctol. 2011;27(3):140-6. https://doi.org/10.3393/jksc.2011.27.3.140
10. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. Ann Allergy Asthma Immunol. 2017;119(5):422-428.e2. https://doi.org/10.1016/j.anai.2017.08.009
11. Otani IM, Wong J, Banerji A. Platinum Chemotherapy Hypersensitivity: Prevalence and Management. Immunol Allergy Clin North Am. 2017;37(4):663-77. https://doi.org/10.1016/j.iac.2017.06.003
12. Yamauchi H, Goto T, Takayoshi K, et al. A retrospective analysis of the risk factors for allergic reactions induced by the administration of oxaliplatin. Eur J Cancer Care (Engl). 2015;24(1):111-6. https://doi.org/10.1111/ecc.12156
13. Ohta H, Hayashi T, Murai S, et al. Comparison between hypersensitivity reactions to cycles of modified FOLFOX6 and XELOX therapies in patients with colorectal cancer. Cancer Chemother Pharmacol. 2017;79(5):1021-9. https://doi.org/10.1007/s00280-017-3294-9
14. Kim MY, Kang SY, Lee SY, et al. Hypersensitivity reactions to oxaliplatin: clinical features and risk factors in Koreans. Asian Pac J Cancer Prev. 2012;13(4):1209-15. https://doi.org/10.7314/apjcp.2012.13.4.1209
15. Yu Z, Huang R, Zhao L, et al. Safety profile of oxaliplatin in 3,687 patients with cancer in China: A post-marketing surveillance study. Front Oncol. 2021;11:757196. https://doi.org/10.3389/fonc.2021.757196
16. Mori Y, Nishimura T, Kitano T, et al. Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with FOLFOX. Oncology. 2010;79(1-2):136-43. https://doi.org/10.1159/000320613
17. Kim BH, Bradley T, Tai J, et al. Hypersensitivity to Oxaliplatin: An Investigation of Incidence and Risk Factors, and Literature Review. Oncology. 2009;76(4):231-8. https://doi.org/10.1159/000205263
18. Seki K, Senzaki K, Tsuduki Y, et al. Risk factors for oxaliplatin-induced hypersensitivity reactions in Japanese patients with advanced colorectal cancer. Int J Med Sci. 2011;8(3):210-5. https://doi.org/10.7150/ijms.8.210
19. Parel M, Ranchon F, Nosbaum A, et al. Hypersensitivity to oxaliplatin: clinical features and risk factors. BMC Pharmacol Toxicol. 2014;15:1. https://doi.org/10.1186/2050-6511-15-1
20. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27, 2017. US Department of Health and Human Services NIoH, National Cancer Institute. 2017.
21. Azam F, Latif MF, Farooq A, et al. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. Case Rep Oncol. 2019;12(3):728-36. https://doi.org/10.1159/000503095
22. Ichikawa Y, Goto A, Hirokawa S, et al. Allergic reactions to oxaliplatin in a single institute in Japan. Jpn J Clin Oncol. 2009;39(9):616-

20. https://doi.org/10.1093/jjco/hyp070
23. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. Engl J Med. 2004;350:2343-51.
24. Castells M. Desensitization for drug allergy. Curr Opin Allergy Clin Immunol. 2006;6:476-81.
25. Makrilia N, Syrigou E, Kaklamanos I, et al. Hypersensitivity Reactions Associated with Platinum Antineoplastic Agents: A Systematic Review. Met Based Drugs. 2010;2010:207084. https://doi.org/10.1155/2010/207084
26. Okayama T, Ishikawa T, Sugatani K, et al. Hypersensitivity Reactions to Oxaliplatin: Identifying the Risk Factors and Judging the Efficacy of a Desensitization Protocol. Clin Ther. 2015;37(6):1259-69. https://doi.org/10.1016/j.clinthera.2015.03.012
27. Kuruvilla M, Khan DA. Eosinophilic Drug Allergy. Clin Rev Allergy Immunol. 2016;50:228-39.
28. Shibata Y, Ariyama H, Baba E, et al. Oxaliplatin-induced allergic reaction in patients with colorectal cancer in Japan. Int J Clin Oncol. 2009;14:397-401.
29. Bourke CD, Berkley JA, Prendergast AJ. Immune Dysfunction as a Cause and Consequence of Malnutrition. Trends Immunol. 2016;37(6):386-98. https://doi.org/10.1016/j.it.2016.04.003
30. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. JPEN J Parenter Enteral Nutr. 2019;43(2):181-93. https://doi.org/10.1002/jpen.1451
31. Nishihara M, Nishikura K, Morikawa N, et al. Factors Influencing the Appearance of Oxaliplatin-Induced Allergy. B Biol Pharm Bull. 2017;40(12):2105-9. https://doi.org/10.1248/bpb.b17-00400