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REVIEW ARTICLE / DERLEME MAKALE

MANAGEMENT OF DRUG INTERACTIONS IN COLON CANCER PATIENTS

KOLON KANSERI HASTALARINDA İLAÇ ETKİLEŞİMLERİNİN YÖNETİMİ

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ABSTRACT

Objective: *Colon cancer is the third most common cancer type globally and usually occurs at advanced ages. Since the risk of comorbid diseases may also increase with age, colon cancer patients have an increased risk of polypharmacy. Hypertension, chronic obstructive pulmonary disease, diabetes, and cardiovascular disease are the frequently seen comorbidities in cancer patients. Patients who are elderly, have comorbid conditions, and are taking two or more medications are at higher risk for drug-drug interactions (DDIs). Additionally, cancer patients frequently use many drugs such as supportive care drugs for the treatment of side effects of cytotoxic drugs. DDIs may cause therapeutic failure or potentially serious adverse events. determination and evaluation of DDI levels identify the most suitable rational therapy for cancer patients.*

Result and Discussion: *This study has reviewed the drugs used to treat colon cancer (Capecitabine, Fluorouracil, Irinotecan, Oxaliplatin, Bevacizumab, Ziv-Aflibercept, Nivolumab, Pembrolizumab, Ramucirumab, Regorafenib, Larotrectinib, Dabrafenib, Trametinib, Trifluridine and tipiracil, and Encorafenib) and determined the possible drug-drug interactions. This study will help the pharmacists and clinicians to evaluate possible interactions.*

Keywords: *Colon cancer, comorbidity, drug-drug interactions, management, polypharmacy*

ÖZ

Amaç: *Kolon kanseri, dünya çapında en yaygın üçüncü kanser türüdür ve genellikle ileri yaşlarda ortaya çıkar. Yaşla birlikte komorbid hastalık riski de artabileceğinden, kolon kanseri hastalarının polifarmasi riski artmıştır. Hipertansiyon, kronik obstrüktif akciğer hastalığı, diyabet ve kardiyovasküler hastalık, kanser hastalarında sık görülen komorbiditelerdir. Yaşlı, komorbid rahatsızlıkları olan ve iki veya daha fazla ilaç alan hastalar, ilaç-ilaç etkileşimleri (İİE) için daha yüksek risk altındadır. Ayrıca kanser hastaları, sitotoksik ilaçların yan etkilerinin tedavisi için sıklıkla destekleyici bakım ilaçları gibi birçok ilacı kullanmaktadır. İİE'ler terapötik başarısızlığa veya potansiyel olarak ciddi yan etkilere neden olabilir. İİE düzeylerinin belirlenmesi ve değerlendirilmesi, kanser hastaları için en uygun akılcı tedavinin sağlanmasında yardımcı olmaktadır.*

Sonuç ve Tartışma: *Bu çalışmada, kolon kanseri tedavisinde kullanılan ilaçlar (Kapesitabin, Fluorourasil, irinotecan, oksaliplatin, bevasizumab, ziv-aflibersept, nivolumumab, pembrolizumab, ramusirumab, regorafenib, larotrektinib, dabrafenib, trametinib, trifluridin ve tipirasil ve enkorafenib) incelenmiş ve olası ilaç etkileşimleri belirlenmiştir. Bu çalışma eczacıların ve klinisyenlerin olası etkileşimleri değerlendirmesine yardımcı olacaktır.*

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Anahtar Kelimeler: *İlaç-ilaç etkileşimleri, kolon kanseri, komorbidite, polifarmasi, yönetim*

INTRODUCTION

Numbers of comorbidity and prescribed drugs are strong predictors of DDIs in cancer patients. It is estimated that DDIs lead to 2% of hospital admissions [1,2] and approximately 4% of the cancer related deaths occurs due to the effects caused by DDIs [3]. Determination and management of most serious DDI in cancer patients reduce drug-related problems and increase efficacy and compliance of chemotherapy [4]. This study will be helpful for promotion of rational drug use and prevention and management of drug interactions in colon cancer patients. Therefore, the study has reviewed DDIs using Medscape and Lexicomp databases and highlighted the contraindicated, serious and major DDIs.

Clinic and Research Effects

Capecitabine and 5-Fluorouracil

Capecitabine and 5-Fluorouracil are antimetabolites [fluoropyrimidine] used alone or in combination with other drugs [4-8]. They are mainly metabolized via hepatic enzymes. Although capecitabine is a prodrug of fluorouracil there is no significant differences between the frequency of drug interactions [9]. It is well defined that concomitant warfarin and a fluoropyrimidine elevates the INR [international normalized ratio] and causing bleedings. Additionally, there have been a black box warning for the capecitabine for cancer patients >60 years of age. Both Lexicomp and Medscape recommend that patients who are treated with fluorouracil-based treatment should be monitored for elevated INR and for signs/symptoms of bleeding closely when treatment is combined with a vitamin K antagonist [4-8]. Additionally, anticoagulant dose adjustment would be necessary. Alkylating agents and anthracyclines are two anticancer drug groups that have a moderate drug interaction between fluoropyrimidines cause bone marrow myelosuppression [10].

Irinotecan

Salvador-Martín et al. (2018) reported that the greater the number of concomitant drugs administered, the incidence of severe irinotecan-related toxicity incidence was higher due to the drug interactions. Since the CYP enzyme systems is used for the irinotecan metabolism, CYP inhibitor drugs may increase the toxicity of irinotecan. Interactions between CYP3A4 substrates and irinotecan occur frequently. Concomitant treatment with antiepileptics, certain antidepressants, antiretroviral drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to affect irinotecan pharmacokinetics or pharmacodynamics. The combination with the potent CYP3A4 inhibitor ketoconazole was one of the first significant DDIs described for irinotecan [12]. A severe rhabdomyolysis syndrome has been

described in a patient using irinotecan and citalopram [13]. The drug interactions between irinotecan and certain antiepileptics (phenytoin, phenobarbital, and carbamazepine) were evaluated in a population pharmacokinetic model, which suggested that patients using these antiepileptics should receive higher irinotecan doses to reach the same exposure as in patients without using antiepileptics [14]. In addition, an important DDI between irinotecan and the combination treatment with ritonavir and lopinavir, caused by CYP3A4 inhibition resulted in a more than two-fold increase in SN-38 [15].

NSAIDs and proton pump inhibitors are frequently used in cancer patients. Irinotecan drug interactions with celecoxib and omeprazole have been evaluated and it was investigated that the coadministration of irinotecan and celecoxib described an increased clearance of irinotecan [16]. A clinically relevant pharmacokinetic interaction between omeprazole and irinotecan was ruled out in a small crossover study [17]. The effects of St. John's wort, cigarette smoking, and cannabis tea on irinotecan pharmacokinetics have been investigated. Concomitant use of St. John's wort and cigarette smoking resulted in a significant reduction of SN-38 AUC, primarily caused by CYP3A4 induction [18]. In addition, (medicinal) cannabis can induce CYP3A4 and inhibit ABCB1, but no interaction was demonstrated between irinotecan and medicinal cannabis tea [19], other cannabis formulations contain different concentrations of the enzyme-modulating compounds. Therefore, it remains unclear if cannabinoid oils are safe in combination with irinotecan [18]. The reduced creatinine clearance is associated with irinotecan-related severe toxicities [20]. Incidence of grade 3 or 4 irinotecan-induced neutropenia has been reported in patients with impaired renal function [20]. Table 1 presents commonly seen drug interactions with irinotecan [23, 24].

Oxaliplatin

Since nephrotoxicity and neurotoxicity are the mainly dose-limiting side effects of oxaliplatin it should be used carefully in patients of old age or patients with renal impairment, neuropathy, neurotoxic agents [25, 26]. Oxaliplatin does not significantly inhibit CYP450 isoforms and therefore, drug-drug interactions of oxaliplatin on co-administered drugs cleared by these are not anticipated in the clinic [21, 22]. Additionally, commonly seen drug interactions with oxaliplatin via different mechanisms are gathered in Table 2.

Bevacizumab and Ziv-Aflibercept

Commonly seen drug interactions with bevacizumab via different mechanisms are given in Table 2. There have been no specific drug-drug interaction studies conducted for aflibercept, although population pharmacokinetic analyses found no clinically relevant drug-drug interaction between ziv-aflibercept and irinotecan or fluorouracil [27-30].

Nivolumab and Pembrolizumab

Nivolumab and Pembrolizumab are monoclonal antibodies to programmed cell death-1 protein [PD-1]. Time to steady state levels are 12 weeks for nivolumab and 16 weeks for pembrolizumab and half lives of two drugs over twenty days [31-34].

Table 1. Commonly seen drug interaction with irinotecan via different mechanism [23, 24]

Drugs	**Mechanism**	**Management**	**Database**
Aprepitant	increases serum level of CYP3A4 Substrates [High risk with Inhibitors).	*Risk C: Monitor therapy*	Lexicomp
Dabrafenib	decreases serum level of CYP3A4 Substrates [High risk with Inducers).	*Risk D: Consider therapy modification* If concomitant therapy cannot be avoided, monitor for reduced clinical effects of the CYP3A4 substrate.	Lexicomp
Fosaprepitant Fosnetupitant	increases serum level of CYP3A4 Substrates [High risk with Inhibitors).	*Risk C: Monitor therapy*	Lexicomp
Larotrectinib	increases serum level of CYP3A4 Substrates [High risk with Inhibitors).	*Risk C: Monitor therapy*	Lexicomp
Palbociclib	increases serum level of CYP3A4 Substrates [High risk with Inhibitors).	*Risk C: Monitor therapy*	Lexicomp
Carbamazepine	decreases level or effect of irinotecan by affecting hepatic enzyme CYP2B6 metabolism.	*Contraindicated.*	Medscape
Itraconazole	İncreases serum level or effect of irinotecan by affecting hepatic/intestinal enzyme CYP3A4 metabolism.	*Contraindicated* Strong CYP3A4 Inhibitors may increases serum level of SN-38 [active metabolite for irinotecan products). Contraindicated during and 2 weeks after itraconazole treatment.	Medscape
Lopinavir	İncreases serum level or effect of irinotecan by affecting hepatic/intestinal enzyme CYP3A4 metabolism	*Contraindicated*	Medscape
Rifampin	Decreases serum level or effect of irinotecan by affecting hepatic enzyme CYP2B6 metabolism	*Contraindicated*	Medscape
Ritonavir	İncreases serum level or effect of irinotecan by P-glycoprotein [MDR1) efflux transporter.	*Contraindicated*	Medscape
St John's Wort	Decreases serum level or effect of irinotecan by P-glycoprotein [MDR1) efflux transporter.	*Contraindicated*	Medscape

Clinically, the only significant drug interaction of these two drugs is with─systemic corticosteroids. Corticosteroids may decrease the therapeutic effect of Immune Checkpoint Inhibitors [*Risk D: Consider therapy modification]* [31-34]. Recommendations for management of drug

interaction as: to consider the need for corticosteroids, at doses of a prednisone-equivalent of 10 mg or more per day, during the initiation of immune checkpoint inhibitor therapy. Additionally, the use of corticosteroids to treat immune related adverse events is still recommended [31-34].

Table 2. Commonly seen drug interactions with oxaliplatin and bevacizumab via different mechanism

	Drugs	**Mechanism**	**Management**	**Database**
OXALIPLATIN	5-Aminosalicylic Acid Derivatives	increases myelosuppressive effects of oxaliplatin	Risk C: Monitor therapy	Lexicomp
	QT-prolonging Agents	Oxaliplatin increases QTc-prolonging effects	*Risk C: Monitor therapy* Monitorization for QTc interval prolongation and ventricular arrhythmias of patients used with these combinations.	Lexicomp
	Chloramphenicol [Ophthalmic)	increases adverse effects of oxaliplatin	*Risk C: Monitor therapy*	Lexicomp
	Clozapine	Oxaliplatin increases adverse/toxic effect of Clozapine	*Risk C: Monitor therapy* the risk for neutropenia may be increased.	Lexicomp
BEVACIZUMAB	5-Aminosalicylic Acid Derivatives	increases myelosuppressive effects of bevacizumab and Ziv-aflibercept	Risk C: Monitor therapy	Lexicomp
	Bisphosphonate Derivatives	bevacizumab and Ziv-aflibercept may increase the adverse effects of Bisphosphonate Derivatives.	*Risk C: Monitor therapy* the risk for osteonecrosis of the jaw may be increased.	Lexicomp
	Chloramphenicol [Ophthalmic)	increases myelosuppressive effects of bevacizumab and Ziv-aflibercept	*Risk C: Monitor therapy*	Lexicomp
	Clozapine	bevacizumab and Ziv-aflibercept may increase the adverse/toxic effect of Clozapine	*Risk C: Monitor therapy* the risk for neutropenia may be increased.	Lexicomp

Ramucirumab

Ramucirumab has a long half life of 14 days and time to steady state level is 12 weeks [35]. Clinically significant drug interactions occur with combination of bisphosphonate derivatives [*Risk C: Monitor therapy*] by increasing adverse effect of bisphosphonates. Specifically, the risk for osteonecrosis of the jaw may be increased [35, 36].

Regorafenib

Regorafenib has significant drug interactions with strong CYP3A4 inhibitors [clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and

voriconazole], Breast Cancer Resistance Protein [BCRP] substrates and UGT substrates [methotrexate, fluvastatin, atorvastatin] [37, 38]. Commonly seen drug interactions with regorafenib via different mechanisms are given in Table 3.

Table 3. Commonly seen drug interactions with regorafenib via different mechanism

Drugs	**Mechanism**	**Management**	**Database**
Aprepitant Fosaprepitant Fosnetupitant	increases serum level of CYP3A4 Substrates	*Risk C: Monitor therapy*	Lexicomp
Beta-Blockers	Regorafenib may increases bradycardic effect of Beta-Blockers	*Risk C: Monitor therapy*	Lexicomp
Bisphosphonate Derivatives	Regorafenib may increases adverse effects of Bisphosphonate Derivatives	*Risk C: Monitor therapy* the risk for osteonecrosis of the jaw may be increased	Lexicomp
Calcium Channel Blockers [Nondihydropyridine)	Regorafenib may increases bradycardic effect of Calcium Channel Blockers [Nondihydropyridine).	*Risk C: Monitor therapy*	Lexicomp
Digoxin	Regorafenib may increases bradycardic effect of Digoxin.	*Risk C: Monitor therapy*	Lexicomp
Fusidic Acid [Systemic)	increases serum levels of CYP3A4 Substrates	*Risk X: Avoid combination*	Lexicomp
Grapefruit Juice	increases serum levels of Regorafenib	*Risk X: Avoid combination*	Lexicomp
Rosuvastatin	Regorafenib may increases serum level of Rosuvastatin	*Risk D: Consider therapy modification* Limits dose of rosuvastatin to 10 mg daily when combined with regorafenib. Monitor closely for increased rosuvastatin effects/toxicities [eg, myalgias, rhabdomyolysis) when these agents are combined	Lexicomp
St John's Wort	decreases serum level of Regorafenib.	*Risk X: Avoid combination*	Lexicomp
Warfarin	increases adverse effects of Regorafenib	*Risk C: Monitor therapy* the risk for bleeding may be increased	Lexicomp
Food Interactions	A high-fat meal increases mean area under the curve [AUC) of the parent drug.	Administer after a low-fat meal	Lexicomp

Larotrectinib

Larotrectinib is a substrate of CYP3A4 [major], P-gp and BCRP [39, 40]. Coadministration with a strong CYP3A4 inhibitor may increase larotrectinib's plasma levels and may result in increased incidence of adverse effects. Coadministration with a strong CYP3A4 inducer may decrease larotrectinib's plasma levels decrease its efficacy (Table 4).

Table 4. Commonly seen drug interaction with larotrectinib via different mechanism

Drugs	**Mechanism**	**Management**	**Database**
Aprepitant Fosaprepitant Fosnetupitant	increases serum levels of CYP3A4 Substrates [High risk with Inhibitors).	*Risk C: Monitor therapy*	Lexicomp
CYP3A4 Inhibitors [Strong)	increases serum level of Larotrectinib	*Risk D: Consider therapy modification* If this combination cannot be avoided, reduces larotrectinib dose by 50%. Increase to previous dose after stopping the inhibitor after a period of 3 to 5 times the inhibitor's half-life.	Lexicomp
Fusidic Acid [Systemic)	increases serum level of CYP3A4 Substrates [High risk with Inhibitors).	*Risk X: Avoid combination*	Lexicomp
Grapefruit Juice	increases serum level of Larotrectinib.	*Risk D: Consider therapy modification* If this combination cannot be avoided, reduce the larotrectinib dose by 50%. Following discontinuation of grapefruit juice, resume the previous dose of larotrectinib.	Lexicomp
Triazolam: CYP3A4 Inhibitors [Weak)	increases serum level of Triazolam.	*Risk D: Consider therapy modification* Consider triazolam dose reduction in patients receiving concomitant weak CYP3A4 inhibitors.	Lexicomp

Dabrafenib

Dabrafenib has an important interaction with hormonal contraceptives. Due to the decrease in efficacy of hormonal contraception, an alternative method of contraception is recommended. Coadministration with CYP3A4 [strong inhibitors or inducers] is not recommended [41, 42]. Drugs that increase gastric acid may decrease dabrafenib absorption [43]. Dabrafenib decreases the serum concentrations of warfarin and dexamethasone [43]. Dabrafenib inhibits certain CYP isoenzymes; concomitant use with drugs may result in loss of efficacy of these drugs (Table 5).

Trametinib

Trametinib is a substrate of CYP2C19 [minor], CYP2D6 [minor], CYP3A4 [major], P glycoprotein/ABCB1 [minor] [44, 45]. Due to the trametinib is a CYP3A4 inducer (low level in vitro), interactions with substrates are not anticipated [45]. Commonly seen drug interaction with Trametinib via different mechanism are listed in Table 6.

Trifluridine and tipiracil

Trifluridine and tipiracil is used for the treatment of metastatic colorectal cancer in adults previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological

therapy, and an anti-EGFR therapy [46]. This drug may enhance the immunosuppressants effects of certain drugs [baricitinib, cladribine, fexinidazole, natalizumab, pimecrolimus, topical form of ruxolitinib, tacrolimus] and the combination use of these drugs are contraindicated. Additionally, live vaccinations are avoided during therapy with trifluridine and tipiracil [46].

Table 5. Commonly seen drug interaction with dabrafenib via different mechanism

Drugs	**Mechanism**	**Management**	**Database**
Alfentanil	decreases serum level of Alfentanil	*Risk D: Consider therapy modification* If concomitant use of alfentanil and moderate CYP3A4 inducers is necessary, consider dosage increase of alfentanil until stable drug effects are achieved. Monitor patients for signs of opioid withdrawal.	Lexicomp
Antidiabetic Agents	Dabrafenib decreases therapeutic effect of Antidiabetic Agents.	*Risk C: Monitor therapy*	Lexicomp
Cannabis	Dabrafenib decreases serum level of Cannabis.	*Risk C: Monitor therapy*	Lexicomp
Codeine	Dabrafenib decrease serum level of the active metabolite[s) of Codeine.	*Risk C: Monitor therapy*	Lexicomp
Deflazacort	Dabrafenib decrease serum level of the active metabolite[s) of Deflazacort.	*Risk X: Avoid combination*	Lexicomp
Estriol	Dabrafenib decreases serum level of Estriol [Systemic, Topical).	*Risk C: Monitor therapy*	Lexicomp
Progestins [Contraceptive)	Dabrafenib decreases serum level of Progestins [Contraceptive).	*Risk D: Consider therapy modification* Females of reproductive potential should use an alternative, highly effective, non-hormonal means of contraception during and at least 2 weeks [dabrafenib alone) or 4 months [dabrafenib + trametinib) after discontinuation of dabrafenib treatment.	Lexicomp
QT-prolonging Agents	Dabrafenib increases QTc-prolonging effects	*Risk C: Monitor therapy* Monitorization for QTc interval prolongation and ventricular arrhythmias of patients used with these combinations.	Lexicomp
St John's Wort	decreases serum level of Dabrafenib.	*Risk D: Consider therapy modification* If combined therapy cannot be avoided, monitor closely for decreased therapeutic effects of dabrafenib.	Lexicomp
Vitamin K Antagonists [eg, warfarin):	Dabrafenib decreases serum level of Vitamin K Antagonists.	*Risk C: Monitor therapy*	Lexicomp
Meperidine	Dabrafenib decreases serum level of Meperidine.	*Risk C: Monitor therapy*	Lexicomp
Prednisolone [Systemic) Prednisone	Dabrafenib decreases serum level of Prednisolone and Prednisone	*Risk C: Monitor therapy*	Lexicomp

Table 5 (*continued*). Commonly seen drug interaction with dabrafenib via different mechanism

Drugs	**Mechanism**	**Management**	**Database**
Estrogen Derivatives [Contraceptive)	Dabrafenib decreases serum level of Estrogen derivatives [Contraceptive).	*Risk D: Consider therapy modification* Females of reproductive potential should use an alternative, highly effective, non-hormonal means of contraception during and at least 2 weeks [dabrafenib alone) or 4 months [dabrafenib + trametinib) after discontinuation of dabrafenib treatment.	Lexicomp
Fusidic Acid [Systemic)	increases serum level of CYP3A4 Substrates [High risk with Inhibitors).	*Risk X: Avoid combination*	Lexicomp
Hydrocortisone [Systemic)	Dabrafenib decreases serum level of Hydrocortisone [Systemic).	*Risk C: Monitor therapy*	Lexicomp

Table 6. Commonly seen drug interaction with Trametinib via different mechanism

Drugs	**Mechanism**	**Management**	**Database**
Dabrafenib	enhances adverse/toxic effect of Dabrafenib	*Risk C: Monitor therapy*	Lexicomp
Clozapine	enhances QTc-prolonging effect of QT-prolonging Kinase Inhibitors [Moderate Risk).	*Risk C: Monitor therapy* Monitorization for QTc interval prolongation and ventricular arrhythmias of patients used with these combinations.	Lexicomp
Domperidone: QT-prolonging Agents	enhances QTc-prolonging effect of Domperidone.	*Risk D: Consider therapy modification* Monitorization for QTc interval prolongation and ventricular arrhythmias of patients used with these combinations.	Lexicomp
Fosaprepitant	increases serum level of CYP3A4 Substrates [High risk with Inhibitors)	*Risk C: Monitor therapy*	Lexicomp
Fusidic Acid [Systemic)	increases serum level of CYP3A4 Substrates [High risk with Inhibitors).	*Risk X: Avoid combination*	Lexicomp
• Haloperidol: QT-prolonging Kinase Inhibitors • Olanzapine • Ondansetron • QT-prolonging Antidepressants • QT-prolonging Antipsychotics • QT-prolonging Class IC Antiarrhythmics • QT-prolonging Kinase Inhibitors	enhances QTc-prolonging effect.	*Risk C: Monitor therapy* Monitorization for QTc interval prolongation and ventricular arrhythmias of patients used with these combinations.	Lexicomp

Encorafenib

Encorafenib is indicated for BRAF V600E mutation-positive metastatic colorectal cancer [47, 48]. It acts as a substrate of CYP2C19 [minor], CYP2D6 [minor], CYP3A4 [major], P-glycoprotein/ABCB1[minor] [48]. It is avoided to use combination with CYP3A4 substrate due to the increasing of the serum drugs levels [abametapir, fusidic acid, pimozide, posaconazole]. Encorafenib doses should be decreased when used in combination with moderate and strong inhibitors of CYP3A4 [45]. Grapefruit juice should not be used during encorafenib therapy because serum concentrations of the drug may increase. Hormonal contraceptives - encorafenib drug interaction is avoided due to the decreasing of the serum concentration of hormonal contraceptives [49].

RESULT AND DISCUSSION

Many potential drug interactions exist with in patients with comorbidities [50, 51]. DDIs may affect plasma level of the oral chemotherapy agent or those of other medications [52]. The use of electronic alerts for potentially serious combinations will be useful for health professionals to determine DDIs in cancer patients. Pharmacists should carefully record all medications and check potential drug interactions. They also should take steps to provide the effectiveness of the cancer therapy, to minimize toxicity and to make recommendations for alternative treatments.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there are no actual, potential or perceived conflicts of interest for this article.

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