International Journal of Clinical & Medical Allergy (IJCMA)
ISSN 2332-2799

A Successful Pretreatment with Extended Corticosteroid Infusion in A Case Of an Irinotecan-Induced Hypersensitivity Reaction: Reflections On The Approach

Research Article

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Abstract

The combined therapy of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (called FOLFIRINOX) is the most effective therapy for metastatic gastrointestinal carcinomas. As a keystone of this protocol, Irinotecan rarely can induce immediate hypersensitivity reactions (HSR), which have been managed by desensitization protocols (under certain pretreatment measures). This work represents a case of an irinotecan-induced immediate HSR successfully pretreated with extended corticosteroid infusion. Besides, it reflects on the rationality of such a therapeutic route in managing mentioned HSRs to antineoplastic drugs. This work emphasizes that a prophylactic pretreatment with extended corticosteroid infusion may suppress the HSRs occurrence, shorten the time of the treatment cycle, and avoid the need for a desensitization procedure, which in concert may lead to earlier successful completion of the antineoplastic therapy.

Keywords: FOLFIRINOX, Irinotecan; Metastatic Gastrointestinal Carcinomas; Immediate Hypersensitivity Reactions; Desensitization; Pretreatment; Extended Corticosteroid Infusion.

Introduction

A combination of folinic acid (leucovorin), 5-fluorouracil, irinotecan, and oxaliplatin (called FOLFIRINOX regimen) is considered the most effective chemotherapy for metastatic carcinomas of the gastrointestinal system, including gastric, pancreatic, or colorectal cancers [1-3]. Despite benefits, most neoplastic drugs cause unpredictable immediate hypersensitivity reactions (HSR). These reactions can affect any organ or system and range widely in clinical severity from mild pruritus to anaphylaxis [4-7].

Moderate to severe HSRs during or after the infusion of every key component of this first-line chemotherapeutic combination usually need a cessation of chemotherapy or substitution of the culprit drug to avoid more severe reactions and possible fatalities [2-5]. The sensitivity of a tumor to certain chemotherapeutics and the necessity to choose the most effective treatment for survival, usually do not allow for the selection of alternative chemotherapeutic agents [2-5, 7].

The need for first-line anticancer therapy and HSR overcoming has been at the core of the development of varying attitudes on the decision to rechallenge the patient after such experience, the efficacy of desensitization protocols, and the selection and effectiveness of drugs for premedication [2-6]. Both approaches, the prophylactic premedication and desensitization (under certain premedication measures) to the culprit drug are practicable options that induce a temporary tolerance to the drug responsible for a proven HSR [3-6, 8, 9]. While prophylactic premedication consists of the administration of the antiallergic agent(s) before the (first) antineoplastic medicament infusion independent of the principal treatment, during desensitization, the principal medicament is administered in progressively rising amounts until the therapeutic dose is reached within a few hours [5-7]. Once a patient completed a successful course of desensitization, all subsequent chemotherapy courses were administered in the outpatient facility with desensitization-trained chemotherapy personnel [5].

Being an essential component of the FOLFIRINOX combination, irinotecan is an antineoplastic drug that prevents DNA from

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Received: November 23, 2022
Accepted: December 13, 2022
Published: December 16, 2022

Citation: Alketa Bakiri, Daniela Bega, Ervin Ç Mingomataj. A Successful Pretreatment with Extended Corticosteroid Infusion in A Case Of an Irinotecan-Induced Hypersensitivity Reaction: Reflections On The Approach. *Int J Clin Med Allergy.* 2022;07(02):81-84.

unwinding by inhibition of topoisomerase I [3, 4]. This agent causes rare IgE-mediated HSRs, usually managed by rapid drug desensitization (RDD) regimens [3]. We present the case of a subject affected by pancreas adenocarcinoma who experienced an IgE-mediated HSR to irinotecan and underwent a successful prophylactic premedication with extended corticosteroid doses (avoiding therefore the RDD protocol). Besides, the discussion shows a reflection on the approach.

Case Report

A 54 year old subject has been affected by locally advanced pancreas adenocarcinoma with synchronous hepatic metastases. The CT examination determined the diagnosis, while partial pancreatic resection, removal of local abdominal lymph nodes, and lien followed a successful chemotherapy treatment. In turn, the histopathological examination of chirurgically-provided specimens determined the disease's stage (pT1N0M1). In the past, she did experience only pruriginous urticaria 30 min after penicillin or naproxen treatment.

The neoadjuvant chemotherapy comprised a FOLFIRINOX regimen as a first-line treatment (scheduled in six two-week cycles). All antineoplastic drugs were infused following the oncology department's routine administration protocol's order, dose, and rate (Table 1). About the prophylactic drugs, dexamethasone, pheniramine, ondansetron, and omeprazole were infused 1h before the beginning of antineoplastic treatment, while atropine sc. was administrated after simultaneous infusion of oxaliplatin and leucovorin. Following product labels, the prophylactic medicaments were applied to reduce the risk of an allergic reaction, and adverse toxic effects of major significance (including cholinergic acute syndrome) [6, 10].

During the first infusion of irinotecan alone (80 minutes after application), the patient manifested dyspnea with prominent labial and lingual angioedema (resolved with adrenaline, glucocorticoids, antihistamines, and oxygen therapy). Then, she tolerated the FOLFOX regimen, indicating an HSR towards irinotecan. Since the irinotecan was inevitable to treat the disease, the allergist proposed either a 12-step RDD protocol [11] or prophylactic pretreatment with extended corticoid doses and antihistamines 1h before the antineoplastic infusion. Given that a kind of premedication was necessary for both protocols and that the RDD protocol had to last for 6h (instead of 1.5h) [5, 11], the patient (via written consent) and oncologist approved the second alternative. Solutions administration and patient supervision followed in an oncology service by well-trained staff. Thus, the subject received a second dose of irinotecan at a slower infusion rate preceded by the pretreatment with an extra dose of methylprednisolone 40mg iv. The subject reported light angioedema in the same corporal regions (resolved by further 40mg methylprednisolone). Next, a prophylactic dose of 80mg methylprednisolone iv. (collectively with dexamethasone, a dose equal to 180mg prednisolone), and 10mg of cetirizine preceded the third dose of irinotecan. This time, the pretreatment procedure was successful and the patient tolerated three additional immunotherapy cycles using this regimen without HSR episodes.

Discussion

Every infusional chemotherapy agent can cause HSRs and those reactions have limited their use since a further application can induce a more severe reaction and possibly death [5, 12]. The HSRs reach a frequency of 5-27% for platins, 10-30% for taxanes, 0.6-10% for specific monoclonal antibodies, etc. [3, 13]. According to Çakmak et al., about 14% of patients experience HSRs during the first chemotherapeutic cycle [7]. Yet, the HSRs of irinotecan are less frequently observed, affecting less than 6% of treated patients [3, 14].

Under prophylactic protocols, irinotecan RDD has been successfully considered even after severe HSRs when substituting another antineoplastic drug was not feasible [3, 4, 7]. The prophylactic pretreatment comprises ondansetron, antihistamines, and 12mg dexamethasone, which precede the 12-step RDD protocol [2, 4, 8, 11]. In this context, rechallenging the patient can be considered an option only after the symptoms have completely resolved [2, 15].

Despite the induction of a temporary toleration state and the accompanying premedication, the occurrence of breakthrough adverse reactions (BTRs) during RDD with various antineoplastic agents is observed in 10-40% of cases [11, 16], and their severity is significantly associated with initial HSR severity, history of drug allergy, and previous exposure to chemotherapeutic agents [3]. It is estimated that 1.3% to 3% of the RDD protocols are not completed because of anaphylactic reactions [7, 16]. About irinotecan, only three cases of RDD are described without any reaction during the protocol, all of them under antiallergic pretreatment

Table 1. The initial protocol of antineoplastic therapy

Treatment type	Medicament	Dose (mg/m²)	Dose (mg)	Therapy duration
Prophylactic	Dexamethasone Pheniramine	-	12	15min, both administrated 1h before the beginning of antineoplastic therapy
		-	45.5	
	Ondansetron	-	8	15min
	Omeprazole	-	40	15min
Antineoplastic	Oxaliplatin	85	167.5	2h, simultaneous administration
	Leucovorin	400	788.2	
Anticholinergic	Atropine	-	0.5	-
	Irinotecan	180	360	90min
Antineoplastic	5-Fluorouracil 5-Fluorouracil	400 2400	788.2 4729	5min, bolus 46h, beginning after bolus administration

measures [3, 4].

The prophylactic pretreatment protocols may comprise the administration of different histamine H1 and H2 receptor blockers, glucocorticoids, montelukast, and acetylsalicylic acid on the day(s) before and during the RDD [3-5, 16]. These protocols differ only in terms of premedication; in the first case, it consists only of antihistamine therapy with or without corticosteroids, while, in the second one, the pretreatment includes the oral intake of 500mg acetylsalicylic acid and 10mg montelukast [3, 4]. Of key importance, the post hoc analysis did not identify any impact of the type of premedication on the treatment efficacy on progression-free survival and overall survival times [6]. About the first approach, the incidence of HSRs was lower in the group of patients who received antihistamine plus corticosteroid (9.6%) compared with those who received antihistamine alone (25.6%). A similar trend was seen for grade 3 or 4 HSRs (1.0% for any antihistamine plus corticosteroid vs. 4.7% for patients receiving antihistamine alone) [6]. Coinfusion of dexamethasone with oxaliplatin also is considered to effectively reduce relative HSRs [2, 17]. According to literature reports, the latter approach reduces the BTRs occurrence in comparison to methylprednisolone pretreatment, which suggests the involvement of prostaglandins D2 and leukotrienes in mast cell activation [3, 18]. Yet, Cubero et al. share the opinion that premedication with antihistamines and corticosteroids should be only used in patients who develop repeated HSRs during previous RDD attempts that were preceded by the pretreatment with acetylsalicylic acid and montelukast [4].

In a few cases of antineoplastic therapy, the lack of supplemental pretreatment with (extended) corticosteroid infusions may lead to unfortunate outcomes, such as refusion of 20-step irinotecan RDD after anaphylactic reaction during the 12 and 16-step ones [3], unfatal cardiorespiratory arrests after oxaliplatin [2, 19], and death after cetuximab treatments [6, 20]. In fact, corticosteroids play a secondary role in the acute phase of anaphylaxis due to their comparatively slow onset of action [21, 22]. Their therapeutic dose varies between 1 and 2mg/kg body weight (BW) for prednisolone to 0.15-0.2mg/kg BW for dexamethasone. Different reviews postulate a non-specific membrane-stabilizing effect within 10–30min of administration of very high corticosteroid doses (in adults, 500–1000mg independent of the substance potency) [21-23]. However, different observations demonstrate that platin-derivates cause HSRs despite the standard pretreatment (12mg dexamethasone and antihistamines) before the RDD procedure [2, 24]. While extended steroid premedication even avoided the severe HSRs, allergic symptoms returned in the following cycle when the subject did not receive corticosteroid therapy [2, 25, 26].

These findings show that, together with antihistamines, the extensive steroid infusions on the day of the RDD procedure [dexamethasone up to 0.3mg/kg BW or (methyl)prednisolone up to 2mg/kg BW] can be employed for safety in patients after (severe) HSRs [2, 4]. Like our case, Thomas et al. support the opinion that patients who develop mild to moderate allergic and infusional reactions can be rechallenged safely after pretreatment with such steroid infusions and antihistamines without an RDD procedure [24].

Collectively, the need for shorter RDD protocols [7, 16, 27], being the pretreatment with 12mg dexamethasone an integral part of RDD [2-5, 8], the HSRs occurrence during the RDD despite such a pretreatment in a large proportion of the affected subjects [3, 11, 16], and the possibility to administrate very high corticosteroid doses during any severe HSR as reported by Ring et al. [21], may suggest us the direct prophylactic administration of (methyl) prednisolone up to 3-4mg/kg BW in case of severe HSRs to any FOLFIRINOX component (Mueller: grade III-IV [28], Ring & Messmer: grade II-IV [29], or Bakiri & Mingomataj: grade IIIA-IV [30, 31]]) skipping the antecedent introduction of an RDD protocol. Some authors, like Bano, Nisi, and their relative collaborators support such a courageous therapeutic route, affirming that an extended corticosteroid premedication with slower oxaliplatin infusion can be employed for safety in patients in cases of severe HSR to oxaliplatin [2, 25]. The quite shorter or avoidance of RDD protocols may allow the use of (methyl)prednisolone as a pretreatment agent, which shows a shorter suppressive effect on the cortex of the adrenal gland. In contrast, the quite longer RDD protocols developed by Castells et al. [11] need the pretreatment with dexamethasone because of the longer plasmatic half-life [32]. In our allergological experience, the casuistic use of methylprednisolone 3-4mg/kg BW together with antihistamines and gastric protectors has prevented the occurrence of any immediate BRT during the single application of medical agents like radiocontrast media, etc., despite experiencing severe HSRs in the previous exposures (data not shown).

Conclusion

Albeit in a small number of patients, it is a pity that the oncologist teams are constricted to stop any component of the FOLFIRINOX regimen after any BRT occurred during the RDD (despite the respective prophylactic therapy). Our case shows that implementing a pragmatic and promising approach to prophylactic premedication with both antihistamines and corticosteroids may suppress the HSRs occurrence, shorten the time of the treatment cycle, and avoid the need for RDD, which in concert may lead to earlier successful completion of the FOLFIRINOX therapy. Consequently, collaboration between oncologists and allergists in assessing and managing HSRs, RDD, and pretreatments is necessary to prevent discontinuing any chemotherapeutic drug. Indeed, any of mentioned protocols should be always evaluated as an individualized possible therapeutic route in subjects with HSRs. Additionally, the mentioned professional staff should perform and supervise the respective procedures in a specialized and safe setting. Still, more prospective randomized studies are necessary to propose individualized pretreatments and RDD protocols in accordance with patient-specific risk stratification. At least the investigation of whether particular corticosteroids might be more effective than others in reducing the incidence of any FOLFIRINOX-associated HSRs would be feasible.

Authors' Contribution

AB and DB managed the patient from the allergological and the oncological point-of-view, respectively; both authors also contributed with helpful discussions. EÇM ideated and drafted the manuscript.

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