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Case Series of Irinotecan-Induced-Dysarthria: A Review of Literature and Proposition of a Pre-Medication Regimen

ABSTRACT

Irinotecan is a topoisomerase-I inhibitor that is commonly used in combination with other chemotherapy agents for gastrointestinal malignancies. It has been found to induce transient dysarthria during infusion which has prompted premature cessation. We encountered 3 patients on FOLFIRINOX who experienced dysarthria-like symptoms during irinotecan infusion. Through a literature review and prospective observational study done at our tertiary care facility, we devised a pre-medication regimen which included extending the irinotecan infusion to 3 hours, replacement of all electrolytes to the upper limits of normal and the addition of atropine during infusion. These steps were to be taken in addition to the standard pre-medications to prevent known side effects of nausea, diarrhea and cholinergic syndrome. During subsequent irinotecan infusion sessions for our 3 patients, we exposed them to our proposed pre-medication regimen which resulted in toleration of therapy and dysarthria-free or significant attenuation of symptoms. The purpose of this case series is to promote further awareness of this unusual reaction as well as to propose a standard pre-medication regimen with all subsequent irinotecan administrations in the event a patient develops dysarthria on initial therapy.

Keywords: Irinotecan-Induced-Dysarthria; Adverse Effect; FOLFIRINOX; Irinotecan; Dysarthria; Pre-Medication regimen

Abbreviations: CSF: Cerebrospinal Sluid; ADR: Adverse Drug Reaction

INTRODUCTION

Irinotecan has emerged as one of the most commonly used chemotherapy agents for gastrointestinal malignancies when used in combination with other agents. It is a topoisomerase I inhibitor that directs its effects during DNA replication and division. This inhibition is led by its active metabolite, SN-38, which has 1000 times more activity than irinotecan itself [1]. This metabolite is where the efficacy as well as the toxicity and adverse effects of irinotecan are thought to be derived from. The frequencies of these deleterious effects are reported for both single-agent and combination use of irinotecan. They include early and delayed diarrhea, nausea, alopecia, electrolyte abnormalities, myelosuppression and acute cholinergic syndrome [2]. One of the less common side effects is a phenomenon of acute onset dysarthria during irinotecan infusion. Causation has been widely

speculated, but the pathogenesis remains largely unknown. Patients typically describe it as an inability to speak as well as tongue swelling and numbness. Interestingly, these symptoms resolve following completion or premature cessation of irinotecan infusion without intervention.

There have been multiple case reports which have reported dysarthria during irinotecan infusion. The area of interest has mainly focused on developing an effective pre-medication regimen. Through a retrospective and prospective analysis, we propose a pre-medication regimen with all subsequent irinotecan administrations in the event a patient develops dysarthria. Herein, we present 3 cases of irinotecan-induced dysarthria and the subsequent mitigation and/or resolution of similar symptoms following institution of our proposed pre-medication regimen.

CASE SERIES

Case 1

A 66-year-old female with a past medical history of hypertension, insulin dependent diabetes mellitus and hyperlipidemia was newly diagnosed with stage IV ductal adenocarcinoma of the pancreas. She initially presented with right upper quadrant abdominal pain and underwent a cholecystectomy, however her pain persisted. Further work up with imaging revealed a pancreatic tail mass as well as low density hepatic masses concerning for metastases. She then underwent an endoscopic ultrasound-guided pancreatic biopsy which revealed pancreatic adenocarcinoma. She was started on palliative chemotherapy with FOLFIRINOX which included 5-fluorouracil 1200 mg/m²/day for 2 days; oxaliplatin 85 mg/m²; leucovorin 400 mg/m²; and irinotecan 165 mg/m². Prior to the chemotherapy infusions, she received the standard pre-medication regimen that included palonosetron 0.25 mg, dexamethasone 12 mg, fosaprepitant 150 mg and atropine 0.4 mg. Approximately 30 minutes into her first irinotecan infusion, she complained of left eye twitching and slurred speech. Infusion was promptly stopped, and her symptoms resolved. Irinotecan was re-challenged with reoccurrence of her symptoms and was not able to complete her first cycle. Of note, she did not experience any similar symptoms with infusions of the other medications. Following her second infusion cycle approximately 2 weeks later, we applied our pre-medication regimen, including extension of the irinotecan infusion to 3 hours, replacing all her electrolytes to the upper

limits of normal and addition of atropine during infusion. She was found to tolerate the infusion with no signs of dysarthria or blepharospasm. These symptoms did not reoccur with future infusions, though irinotecan was eventually discontinued due to persistent nausea as well as a persistent decline of her performance status.

Case 2

A 61-year-old male with a remote history of tobacco abuse was recently diagnosed with stage I adenocarcinoma of the proximal body and neck of the pancreas. He initially presented with epigastric pain that radiated to his back, poor appetite and weight loss. Imaging revealed an ill-defined mass near the mid-body of the pancreas. The patient was referred for an endoscopic ultrasound-guided pancreatic mass biopsy which revealed pancreatic adenocarcinoma. Treatment was initiated with neoadjuvant FOLFIRINOX using the standard dosing and regimen to prevent known side effects described for **Case 1**. He completed his first infusion therapy with no complications. During his second cycle, he reported symptoms of slurred speech and hoarse voice which occurred immediately following the completion of the irinotecan infusion. His symptoms resolved without intervention after approximately 30 minutes. Prior to his third cycle, we administered our pre-medication regimen as described above. During his infusion, he did complain of dysarthria-like symptoms but noted they were significantly less in severity and shorter in duration than his previous episode and resolved quickly. He was also noted to experience symptoms of dysarthria during his next 2 cycles but again, reported his symptoms were significantly reduced when compared to his initial episode.

Case 3

A 66-year-old female with no reported past medical history was recently diagnosed with stage IV adenocarcinoma of the head and neck of the pancreas. She initially presented for further evaluation of jaundice with imaging concerning for a pancreatic mass with subsequent endoscopic ultrasound-guided biopsy confirming pancreatic adenocarcinoma. The patient was initiated on palliative FOLFIRINOX therapy and as in **Case 2**, this patient tolerated the first cycle. However, following her second cycle of irinotecan, she complained of slurred speech which resolved after approximately 30 minutes without intervention. We instituted our proposed pre-medication

regimen for this patient and she has since received 9 cycles of FOLFIRINOX without any reoccurrence of dysarthria-like symptoms.

DISCUSSION

Our 3 cases demonstrated the classic manifestation of irinotecan-induced dysarthria. To our knowledge, there have been 13 similar cases documented. A select number of these cases have attempted similar or different pre-medication regimens for prevention and/or mitigation of such symptoms. We sought to investigate their respective reasonings for each regimen and attempt to create a standardized regimen to mitigate the symptoms surrounding irinotecan infusion. In addition, we attempted to further categorize the pathophysiology surrounding this dysarthria phenomenon.

A well-known potential adverse effect of irinotecan is acute cholinergic syndrome, for which atropine prior to infusion has become standard of care. This syndrome is believed to be mediated by the active metabolite of irinotecan, SN-38, which binds and inhibits anticholinesterase [3]. This increase of cholinergic stimulation is what has been postulated as one of the mechanisms for dysarthria in this population of patients, [4] although no data regarding the pharmacokinetics of irinotecan or SN-38 in the cerebrospinal fluid (CSF) has been studied. Blaney et al. [5]. However, found that approximately 14% of irinotecan, not SN-38, was found in the CSF of non-human primates. Nevertheless, for both to potentially induce these symptoms, it is also suggested that they do indeed cross the blood brain barrier causing an imbalance of neurotransmitters through inhibition of anticholinesterase [6]. Regarding the plasma concentrations, both irinotecan and SN-38 levels have been found to peak following completion of irinotecan infusion with SN-38 also being detected soon after initiation of infusion [7]. These findings correlate clinically with many of these patients developing symptoms soon after initiation of infusion and resolution soon after. Given these findings, we felt that the standard dosage of atropine we were providing to our patients prior to infusion was likely suboptimal. Also, given the fact that SN-38 has been found to peak during mid to late cycle infusion of irinotecan, we added another dose of atropine 0.4 mg during infusion. We have since found that our patients have tolerated this without any of the known adverse effects. It has also been efficacious in the amelioration of dysarthria-like symptoms in addition to the remainder of the pre-medication regimen.

The extension of irinotecan infusion has also been reported in prior cases as another means of mitigating or alleviating dysarthria in this subset of patients. The standard duration of irinotecan infusion is typically 30 min to 120 min. In our practice, we initially start the patients on a duration time of 120 minutes. There have been 2 prior cases documented where the infusion time was increased to be greater than 120 minutes and in both cases, the level of dysarthria was mitigated but did not resolve completely [8,9]. Knowing that SN-38 quickly accumulates in the plasma during infusion resulting in high plasma distribution, we sought to increase the duration of infusion to prevent such a resultant large plasma level of the irinotecan metabolite. Given this, we have increased the infusion time to 180 minutes.

Checking and replacing a patient's electrolytes to the upper-limits of normal prior to infusion has been observed to also mitigate further dysarthria-like symptoms. The source of the low levels of electrolytes is likely secondary to known side effects such as vomiting and diarrhea. However, the mechanism by which this electrolyte imbalance could promote such a neurological side effect is still unknown. Basso et al. [10] hypothesized that oxaliplatin, which is included in the FOLFIRINOX regimen, may interfere with calcium-dependent potassium channels by reversibly blocking their activity which hypokalemia may further exacerbate. A prior case of dysarthria following FOLFIRINOX therapy found a patient to be hypokalemic at 1.7 mEq/l and another case described a patient who was both hypokalemic at 3.1 mEq/l and hypomagnesemic at 0.37 mmol/l [10,11]. Another case of dysarthria following therapy was also found to have mild hypokalemia of 3.5 mEq/l. Prior to their following cycle, their potassium level was checked and corrected to 4.4 mEq/l and they subsequently no longer experienced dysarthria symptoms [12]. The severity of the electrolyte imbalance in relation to the adverse effects is unknown, but due to the concerns of peripheral toxicity, we have implemented a replacement protocol where electrolytes are replaced to the upper limits of normal prior to FOLFIRINOX therapy.

Fasting prior to irinotecan has also been proposed to prevent the side effects associated with the medication. Huisman et al. [13] examined the effects of fasting prior to irinotecan in mice with intestinal tumors. They divided the cohorts into fed and 3-day fasted mice prior to treatment. They found that

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	+2
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total Score:				9

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-245.

the fasting mice developed significantly less adverse effects such as weight loss, lower activity, diarrhea and leukopenia when compared to their counterparts with no negative effect to irinotecan's anti-tumor activity. No cases to date have observed this method in humans but it serves as a potential addition to the pre-medication regimen or possible alternative to those unable to tolerate such a regimen.

Based on prior cases, we opted to forgo imaging of the brain for all 3 of our cases. The localized and isolated complaints of the symptoms reported as well as no other neurological deficits found on examination, made it clear that they were not due to an intracranial process but rather irinotecan-induced. Application of the adverse drug reaction (ADR) probability scale of Naranjo et al. [14] in this case yielded a score of 9, indicating a definite ADR caused by irinotecan.

Through our literature review, we found that irinotecan-induced-dysarthria can be managed through various methods. We compiled and propose a premedication regimen which has thus far been successful in preventing irinotecan-induced-dysarthria. Awareness and knowledge of the management of this unusual reaction can prevent premature discontinuation of an effective chemotherapy regimen.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with

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