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CASE REPORT

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Successful Desensitization in a Pediatric Patient with Cytarabine Anaphylaxis

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ABSTRACT

Cytarabine (ARA-C) is a chemotherapeutic agent used in the treatment of hematologic malignancies. Although infusion reactions are generally observed with ARA-C, IgE and non-IgE-mediated hypersensitivity reactions have also been reported.

Anaphylaxis was observed on the 3rd dose of ARA-C treatment in a 17-year-old patient diagnosed with acute myeloid leukemia. There was no alternative treatment option for his malignant disease, and we decided to conduct ARA-C desensitization.

We would like to describe a successful desensitization protocol in a pediatric patient who experienced anaphylaxis during ARA-C infusion.

Keywords: Desensitization, anaphylaxis, cytarabine (ARA-C)

INTRODUCTION

Cytarabine (ARA-C) is a chemotherapeutic agent used in the treatment of acute myeloid leukemia (AML) and non-Hodgkin lymphoma (1). ARA-C is a nucleoside analog that acts intracellularly and inhibits DNA synthesis by transforming into cytidine triphosphate. As an antimetabolite, it acts on cells in the S phase of the cell cycle to inhibit the elongation of DNA chains and triggers the cells to enter the apoptotic phase, thereby promoting faulty DNA synthesis (2).

There are several reports of adverse drug reactions in patients receiving ARA-C treatment. Myelosuppression, irritation at the site of administration, gastrointestinal side effects, stomatitis, conjunctivitis, reversible liver enzyme elevation, and dermatitis are some of the most common adverse reactions reported for ARA-C; cerebral and cerebellar toxicity may also occur during intrathecal administration. Most of these adverse effects are type A reactions due to the pharmacologic effects of the drug. Cytarabine syndrome is characterized by nonspecific symptoms, such as fever, malaise, rash, arthralgia, and myalgia, occurring shortly after cytarabine administration, which can be controlled with corticosteroids (3). In addition, immunoglobulin-E (IgE) and non-IgE-mediated hypersensitivity reactions (HSRs) have been identified with ARA-C use (4-6). HSRs usually occur during or within a few hours after the end of drug infusion, although it is possible to observe nonimmediate reactions that appear afterward by hours or days after the end of administration. Cutaneous manifestations, such as flushing and/or pruritus, which can progress to urticaria, angioedema, and widespread erythema are the most common symptoms. Involvement of the respiratory and/or gastrointestinal tracts can follow the initial cutaneous symptoms. In severe cases, hypotension, cardiovascular collapse and even death can occur (7).

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Anaphylaxis with ARA-C is a rare occurrence, with limited evidence reported in the literature (6). In general practice, anaphylaxis is an indication for drug discontinuation; however, if the drug is vital for the patient and there are no other alternatives, drug desensitization is attempted (7). There is a paucity of literature regarding desensitization with ARA-C, most of which is related to adult patients (4,5). Herein, we present a case of pediatric anaphylaxis to ARA-C successfully managed by desensitization.

CASE PRESENTATION

Three years ago, a 17-year-old male patient underwent hematopoietic stem cell transplantation (HSCT) for the treatment of aplastic anemia. In April 2024, he was admitted to our hospital for thrombocytopenia. We performed bone marrow aspiration and found that the flow cytometric features of the blast cell population were consistent with the AML M0 subtype. Accordingly, a second HSCT was planned for the patient.

Initially, decitabine and venatoclax treatments were applied due to concerns about the high toxicity associated with traditional chemotherapies. Before initiating HSCT, we decided to administer a 100 mg/m^2/dose of ARA-C every 12 hours, twice daily, intravenously (30-minute infusion), similar to the induction therapy (ARA-C/idarubicin/etoposide [AIE]) used in the AML–Berlin-Frankfurt-Münster (AML-BFM) protocol. While the patient was receiving the 3rd dose of ARA-C, he developed shortness of breath, wheezing, flushing, and angioedema (in the ears) after 20 minutes of infusion. On physical examination, his body temperature was 36.1°C, pulse was 143/min, blood pressure was 120/90 mmHg, and oxygen saturation was 94%.

Due to the patient's respiratory and skin symptoms after probable allergen exposure he clinically met the criteria for anaphylaxis (8). Drug administration was stopped. Intramuscular adrenaline was injected as an anaphylaxis treatment, and the patient's symptoms regressed. Additionally, he was given an antihistamine and methylprednisolone for angioedema and flushing and an inhalable short-acting β-2 agonist for respiratory symptoms. Skin prick test (SPT) with ARA-C could not be performed because the patient was given antihistamines due to skin findings at the time of anaphylaxis and was required to continue the treatment regimen. The tryptase level at the time of the reaction was 9 ng/ml.

Since the ARA-C treatment was vital for the patient, and there was no other alternative, we decided to perform desensitization. The process was explained to the patient and his parents, and written consent was obtained prior to the procedure. The desensitization process was carried out in an appropriate setting with emergency intervention facilities and under the direct supervision of healthcare personnel proficient in managing hypersensitivity reactions.

A 16-step desensitization protocol with four ARA-C solutions (4 steps for each solution: 0.001 mg/mL, 0.01 mg/mL, 0.1 mg/mL, and 1 mg/mL) was performed in 5 hours and 7 minutes with hydroxyzine premedication (Table I). No adverse reactions were observed during or after the infusion. The patient received 12 doses of ARA-C after desensitization without any problems (given at 12-hour intervals). The remaining doses were given at the routine infusion time so that the doubling of the half-life was not exceeded.

DISCUSSION

Anaphylaxis is a sudden, life-threatening systemic hypersensitivity reaction. With the widespread use of chemotherapeutic agents, anaphylaxis has been reported with chemotherapeutics. The most commonly used chemotherapeutic agents are platinum and taxanes, epipodophyllotoxin, procarbazine, and L-asparaginase; however, anaphylaxis can occur with any agent (9).

Although there are reports of anaphylaxis due to ARA-C, there is insufficient information on ARA-C desensitization, especially in pediatric patients. Albanesi et al. described two adult cases of late cutaneous reactions with ARA-C, for whom desensitization was achieved with a 12-step, four-solution subcutaneous protocol of increasing the full dose every other day for 24 days (4). Akgül Balaban et al. reported the use of a 12-step, three-solution desensitization protocol applied to a 47-year-old male patient diagnosed with a non-IgE-mediated infusion reaction (5). Lim et al. also reported successful desensitization in 2 adult patients who had infusion reactions (10). There is also a case of adult anaphylaxis reported by Rassiga et al. in 1980, in which ten milliliters of 0.002% ARA-C were slowly administered intravenously, this sequence being repeated until treatment was initiated with 200 mg ARA-C per 500 mL of saline (11). The only pediatric case available in the literature is the use of a 13-hour long three-solution desensitization protocol in a 9-year-old female patient who described an early reaction, in 1997 (6).

Table I. Intravenous Desensitization Protocol of ARA-C.

Step	Solution type	Concentration	Volume infused per step (mL)	Infusion rate (ml/hour)	Infusion duration (min)	Dose administered with this step (mg)	Cumulative dose (mg)
1	A	1/1000	0.5	2	15	0.0005	0.0005
2	A	1/1000	1	4	15	0.001	0.0015
3	A	1/1000	2	8	15	0.002	0.0035
4	A	1/1000	4	16	15	0.004	0.0075
5	B	1/100	1	4	15	0.01	0.0175
6	B	1/100	2	8	15	0.02	0.0375
7	B	1/100	4	16	15	0.04	0.0775
8	B	1/100	8	32	15	0.08	0.1575
9	C	1/10	2	8	15	0.2	0.3575
10	C	1/10	4	16	15	0.4	0.7575
11	C	1/10	8	32	15	0.8	1.5575
12	C	1/10	16	64	15	1.6	3.1575
13	D	1/1	4	16	15	4	7.1575
14	D	1/1	8	32	15	8	15.1575
15	D	1/1	16	64	15	16	31.1575
16	D	1/1	110	80	82	110	141.1575

Note: Solution A: 1/1000 (0.001 mg/mL). Solution B: 1/100 (0.01 mg/mL). Solution C: 1/10 (0.1mg/mL). Solution D: 1/1(1 mg/mL).

2 cc (200 mg) is taken from ARA-C and is diluted with 198 cc of SF, resulting in 200 cc → Solution D;

5 cc of Solution D is taken, and 45 cc of SF is added, resulting in 50 cc → Solution C;

5 cc of Solution C istaken, and 45 cc of SF is added, resulting in 50 cc → Solution B;

5 cc of Solution B is taken, and 45 cc of SF is added, resulting in 50 cc → Solution A.

The process of desensitization involves modifying the patient's reaction to the drug to create tolerance. In the literature, adult protocols with ARA-C either applied large volumes of fluids (11) or applied to late cutaneous reactions (4) and infusion reactions (5,10). The only pediatric protocol was 13 hours long (12). Since there are not enough examples in the literature, the protocol used for our patient was based on the desensitization principles developed by Castells et al. and the recommendations of the European Drug Allergy Network/European Academy of Allergy and Clinical Immunology regarding rapid drug allergy desensitization (12). Our patient was able to take his medication without any problem with a four-solution, 16-step protocol. We chose a long 16-step protocol because the initial reaction findings were compatible with anaphylaxis, and there are not enough pediatric protocols reported in the literature. Furthermore, there is a lack of distinction between infusion reactions and hypersensitivity reactions. Infusion reactions usually occur with the first dose, whereas allergic reactions usually occur with subsequent doses because a sensitization period is required. Nonspecific symptoms such as fever, fatigue, arthralgia, and myalgia are more prominent in infusion reactions, while our patient developed wheezing, flushing, and angioedema on his 3rd dose. He met the criteria for anaphylaxis due to respiratory system and skin involvement (8). Nevertheless, ARA-C desensitization has been shown to be effective for both hypersensitivity reactions (immediate and delayed types) and infusion reactions (4-6,10,11).

Although there is no definitive recommendation for children regarding premedication in rapid drug desensitization, chemotherapeutic agents' own premedications can be applied. Pretreatment regimens depend on the experience and preferences of individual centers and aim to prevent or minimize breakthrough reactions that occur during rapid drug desensitization. Antihistamines (H1 and H2 blockers) and corticosteroids are included in most pretreatment protocols (13). There was no routine premedication for ARA-C; we preferred antihistamines due to skin findings in our patient.

CONCLUSION

In conclusion, desensitization provides an opportunity to continue drug treatment in patients who clinically need anticancer drugs. In this case report, desensitization therapy was the only option, as ARA-C administration was contraindicated due to anaphylaxis, and no alternative medications were available or were less effective. Nevertheless, the desensitization process should be performed under the supervision of allergists at centers with appropriate emergency intervention facilities.

Conflict of Interest

The authors have no relevant financial or non-financial interest to disclose.

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Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. This is an observational study. The Ethics Committee has confirmed that no ethical approval is required.

Authorship Contributions

Concept: **Zeynep Şengül Emeksiz, Emine Dibek Mısırlıoğlu,** Design: **Emine Dibek Mısırlıoğlu,** Data collection or processing: **Funda Aytekin Güvenir, Emre Sefa Gültekin,** Analysis or Interpretation: **Zeliha Güzelküçük, Namık Yaşar Özbek,** Literature search: **Funda Aytekin Güvenir, Zeynep Şengül Emeksiz,** Writing: **Funda Aytekin Güvenir,** Approval: **Namık Yaşar Özbek, Emine Dibek Mısırlıoğlu.**

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