JBUON 2021; 26(6): 2645-2652
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

A new protocol of desensitization for systemic therapy agents in oncology

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Summary

Purpose: *Systemic treatments among other adverse effects, could have allergic reaction, which are challenging for oncologists regarding the continuation of systemic chemotherapy. this prospective study established a new regimen of desensitization such as dilutions, time of infusions and delivery schedule, which could be used for inpatients or in ambulatory patients.*

Methods: *This was a prospective study of patients with moderate to severe allergic reaction to systemic treatment in our Oncological Institute "I. Chiricuta" Cluj-Napoca. A new protocol for desensitization procedure with a three-day regimen with hospitalization on Medical Oncology Department was proposed to these patients. Initial dilution for drug-related allergy was 1:1,000. The following infusion steps (concentrations) were multiplied by 10 if no severe allergic reaction occurred. Each day had 3 perfusions, each of one was passed in a timeframe of 2 h. The last step (dilution) of perfusion of the day 2 and 3 was 1:1 diluted.*

Results: *Eighty-two patients with a median age of 56 years formed the initial cohort. A platin derivate containing regimen was the main cause for an allergic reaction for 75 out of 82 patients. Four of them had a personal history of previous allergic reactions to chemotherapy, and 56 had multiple lines of chemotherapy in their treatment. More than 594 desensitization procedures were administered to included patients, with a failure rate of less than 2%. The main reason for discontinuation was disease progression or adjuvant chemotherapy administration.*

Conclusions: *Having an allergic reaction does not preclude the administration of the responsible drug. A 3-day regimen with starting dilution of 1:1,000 could represent a successful strategy for continuing administration of an essential chemotherapy drug.*

Key words: *allergy, cancer, desensitization, systemic therapy, platinum derivatives*

Introduction

Cancer represents one of the main causes of death in European countries [1,2]. Systemic treatments are part of multidisciplinary treatments in neoplastic diseases in many ways of administration: neoadjuvant, adjuvant (for the curative stage of the disease), or palliative (more advanced or metastatic stage). Over time, the systemic armamentarium has been developed, and new drugs are available for clinical use. Administered in monotherapy or combinations, systemic drugs could cure a supplementary 20% of patients diagnosed with cancer when compared with surgery alone [3,4].

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Received: 30/08/2021; Accepted: 13/10/2021

World Health Organization each year releases a list of essential drugs where cytotoxic compounds are among them [5]. The side effects of systemic chemotherapy or targeted therapy are general or class-related – for example, hematologic, hepatic, renal toxicities, and so on. A general side effect could be represented by an allergic reaction at first or after multiple administrations (multiple rechallenges for a long and relapse-linked history of disease). In case of an allergic reaction, depending on the intensity of the response which could be very severe till a life-threatening reaction, the chemotherapeutic regimen needs to be changed or not. For a specific type of cancer, some drugs are essential in their treatment such as platin derivates in ovarian cancer, anthracyclines in soft tissue sarcoma etc.

In case of impossibility of replacing the inflicting medicine or survival decreasing desensitization, the scheme requires change. In the published literature many proposed regimens can be found for both intravenous and oral ways of administration, with different dilution schemes or time-schedule of administration, for hospitalized or outpatients, with or without intensive care surveillance.

The etiology or physiopathological mechanism of an allergic reaction to chemotherapy drugs is largely unknown but depends on the time of onset - acute or delayed - could be represented by an IgE (immunoglobulin E), a type I reaction or respectively lymphocyte T mediated reaction, a type IV allergic reaction [6]. Eligible patients for desensitization protocol are those with clinical response from the previous infusion of the drug or with a skin test reaction. To diminish the risk of an allergic reaction for known antigenic oncological drugs, a premedication is usually recommended to be administered before infusion. This includes diphenhydramine (H-1 blockers) and/or famotidine (H-2 blockers) and corticoids (long-life in the previous administration evening, and short-life immediately before administration). The length of premedication could be different according to institutional protocols from previous and the day of infusion, till 5 days in total. Some published data are suggesting that a short premedication - for paclitaxel for example - could be enough without supplementary risks which remain at 7% [7]. Even more, some authors tried to stop pre-medication if no allergic reaction did not occur after two doses of paclitaxel, with no allergic response reported for the included 55 patients treated for breast cancer.

Methods

The Institutional Ethical Board approved this study (No. 42/8 Dec 2015). A retrospective review of the medical records of all patients diagnosed and treated in our Institute from 2012 to 2019 with systemic therapy and symptomatic allergic reaction and desensitization protocol was performed, and the patients with the following criteria were included in the analysis. All included patient consent before systemic treatment was administered.

Inclusion criteria were: patients with malignant condition confirmed histologically, indication for systemic therapy - curative or palliative (multiple lines of chemotherapies allowed for relapsed disease), allergic reaction to a chemotherapeutic drug with an intensity moderate to severe but not life-threatening, with at least one attempt to follow a desensitization protocol in our Institution. The severity of the reaction was based on the Common Toxicity Criteria, version 4.03 [8].

Through the inclusion and treatment process, the following items considered of interest were collected: age, gender, body mass index (BMI), relapse-free interval, cumulative doses of the inflicted drug for allergic reaction before the allergic incident or till cease of chemotherapy line where used desensitization protocols, values of hematologic and biochemical results, type of cancer and clinical stage of disease, previous lines of chemotherapies, the response through the line using the desensitization protocol.

Our institutional desensitization protocol is detailed in Tables 1 and 2. Epinephrine was immediately available if needed.

Table 1. Premedication protocols pre-admission and during the inpatient period

Period	*Drugs*
Home premedications pre-day of the first infusion (2 drug regimen)	1. Loratadine - 10 mg BID 24 h before protocol, 10 mg 3 h before protocol on the day of chemotherapy administration 2. Medrol - 32 mg BID 24 h before protocol, with omeprazole protection 20 mg BID
Hospital premedication before desensitization protocol each day of infusion (3 drug regimen)	1. Hemisuccinate of hydrocortisone 200 mg IV 30 min before the protocol 2. Ranitidine 50 mg IV 30 min before the protocol 3. Loratadine10 mg per os 30 min before the protocol

Table 2. Oncological Institute Cluj-Napoca drug desensitization protocol for an allergic reaction - 3 days of infusion as an inpatient. Example for carboplatin 600 mg total dose (using the Calvert formula)

Day	*Bag*	*Dilution & time to infusion*	*Calculated dose (mg/bag)*	*Accumulated dose (mg)*
1	1	1/1000 of calculated total dose in glucose 5% infusion for 2 hours	0.6	0.6
	2	1/100 of calculated total dose in glucose 5% infusion for 2 hours	6	6.6
	3	1/10 of calculated total dose in glucose 5% infusion for 2 hours	60	66.6
2	1	1/100 of calculated total dose in glucose 5% infusion for 2 hours	6	72.6
	2	1/10 of calculated total dose in glucose 5% infusion for 2 hours	60	132.6
	3	½ of the remaining total dose of the drug in glucose 5% infusion for 2 hours	[600-(3 X 60 + 3 X 6 + 0.6) /2 = 200.7	333.3
3	1	1/100 of calculated total dose in glucose 5% infusion for 2 hours	6	339.3
	2	1/10 of calculated total dose in glucose 5% infusion for 2 hours	60	399.3
	3	½ of the remaining total dose of the drug in glucose 5% infusion for 2 hours	[600-(3 X 60 + 3 X 6 + 0.6) /2 = 200.7	600 Completed target

In diabetes mellitus, if needed, the chemotherapy agent responsible for the allergic reaction could be dissolved in normal saline except for oxaliplatin. All drugs benefited the anti-emetic therapy according to emesis risk for the regimen. During desensitization protocol, the patients were monitored carefully for vital signs, infusion rate, and dilution, and if applicable the time of hyper-sensitivity reaction.

Our Institute protocol for patients with moderate to severe allergic reaction to a chemotherapeutic agent imposed hospitalization for the first reaction for 24-h period of surveillance on the Medical Oncology Department or Intensive Care Unit (depending on the severity of the reaction). Next, the cycle of treatment was scheduled to be administered as an inpatient with the same pre-medication as a standard infusion but repeated daily. Life-threatening reaction for a drug precluded any desensitization protocol for the incriminating drug in the future, no matter what drug-free intervals were recorded. If a recurrence of allergic reaction occurred, the same Common Toxicity Criteria, version 4.03 were used to grade this incident. Presentation and severity of the adverse event could vary from an initial allergic reaction. The used medication consisted of hydrocortisone 100 mg, ranitidine 50 mg and loratadine 10 mg, while epinephrine was reserved only for severe reaction (bronchospasm, angioedema, or sustained hypotension). Depending on the resolution of the symptoms and the severity of the episode the protocol was resumed at the previous well-tolerated dilution (with the same premedication) for the calculated dose of the drug.

For the subsequent desensitization treatments, the grade of severity of allergic reactions was the main item appreciated by the attending physician to decide the continuation or not of the protochol (intensity must be stable or less than previous treatment).

Results

Eighty-two patients were identified in our Institute with desensitization protocol, between 2012 and 2019. Baseline demographic data are presented in Table 3.

The cohort had an average age of 56 years and about 2/3 were female. Ovarian or fallopian cancer was the most frequent type of cancer (50%), followed by colorectal cancer (CRC) (30.8%), head and neck cancer, while digestive cancers other than CRC and carcinoma of unknown primary(CUP) were represented equally (4.8%). Carboplatin was the most frequent agent to determine a desensitization protocol (51.2%) and taxanes were responsible for 46.3%. The administration of these systemic drugs was for palliative treatment in 91.4%. Of the allergic reaction which determined the initiation of desensitization protocol, the intensity was moderate in 80.1%.

A total of 594 desensitization cycles were administrated with a rate of success of 96.6%.

Table 3. Baseline demographic data of the included patients with a desensitization protocol

Characteristics	*Females*	*Males*	*All*
Gender			
n (%)	61 (74.4)	21 (25.6)	82 (100%)
Age, years			
Average (SD)	55.7 (8.3)	56.7 (10.6)	56.0 (9.1)
Min- max	38-73	32-74	32-74
Body mass index (BMI)			
Average (SD)	27.3 (6.4)	24.6 (4.6)	26.6 (6.1)
Min- max	16-42	18-38	16-42
Intension of treatment (curative / palliative for relapse or metastasis)			
Curative	5	2	7
Palliative	55	20	75
Type of systemic therapy			
Carboplatin	29	13	42
Cetuximab	1	1	2
Taxanes	32	6	38
Line of treatment (palliative)			
<2	38	19	57
>2	22	3	25
Type of cancer			
Ovarian cancer	42	N/A	42
Colorectal cancer	10	15	25
Esophageal & Gastric	4	0	4
Non-small lung cancer	0	2	2
Head & Neck	0	4	4
Cervical carcinoma	1	N/A	1
CUP	3	1	4

CUP: carcinoma of unknown primary, SD: standard deviation.

Table 4. Description of desensitization protocol

Characteristics	*Female*	*Male*	*All*
Number of cycles of chemotherapy received before allergic reaction			
Average (SD)	9.4 (5.9)	8.9 (6.1)	9.3 (6.0)
min-max	1 -32	1-25	1 - 32
Number of desensitization cycles of chemotherapy (594)			
	No AR	With AR	N/A
	574 (96.63%)	20 (3.37%)	10 AR (1.68%) was severe but without ICU intervention but with discontinuation of the protocol
Number of desensitization cycles / patient			
median number (range)	No AR	With AR	N/A
	8.2 (1-60)	2.22 (1-9)	
Reason for stop desensitization protocol (no of patients)			
PD	27	16	43
CD	7	0	7
AR	9	1	10
CR	13	2	15
T	4	3	7

CD: continuing desensitization, AR: allergic reaction, CR: complete remission, T: toxicity other than an allergic reaction.

Table 5. Differences between patients who tolerate or do not the desensitization protocol

Criteria	*No AR*	*With AR*	*p value*
No of desensitization cycles (%)	574 (96.63)	20 (3.37)	<0.001
Median number of cycles (protocol) / (patient) (range)	8.2 (1-60)	2.22 (1-9)	<0.001
The median number of cycles received by the patient before AR which initiated the desensitization protocol	9.70 (1-32)	5.78 (1-9)	0.008
Age, years	55.74	58.33	>0.05
Gender	males and females		>0.05
BMI	26.37	27.82	>0.05

AR: allergic reaction, BMI: body mass index

Ten patients from the selected cohort experienced severe allergic reaction during the desensitization protocol which imposed to stop the protocol. Only 20 cycles from 594 administered were with a moderate or severe allergic reaction. The rate of success of desensitization (no or mild symptoms) was 96.6%.

In an attempt to identify the best candidate for desensitization protocol we performed a statistical analysis to see which are the differences between the failed patients and those who tolerated very well the investigated protocol, which is resumed in Table 5.

Discussion

Desensitization represents a modern and useful tool to overcome an allergic reaction for an essential drug used in systemic treatment for a patient with cancer. Continuing the administration protocol for the patient could be imperative to assure the best chance of survival. This is the case for ovarian cancer patients where administration of platin derivatives combination is essential for overall survival both in adjuvant and in case of platin-sensitive relapse situation.

For desensitization purposes, one or multiple solutions/dilutions could be used which are perfused with different rates. In the following paragraphs, we discuss some particularities regarding the strategies which could be chosen by oncologists.

One solution, multiple steps

A solution protocol presumes that the entire prescribed drug is diluted in one bag, which is administered with a different level of infusion rate. First, it is a very slow rate of perfusion, and according to the patient's tolerance, at fixed time intervals this speed can be increased until the whole dose is administered. Usually, this type of desensitization protocol is performed (at least in the first cycle) in a specialized department – intensive care unit, to assure adequate intervention in case of severe allergy.

Chung et al tried a non-dilution rapid protocol (12 steps of infusion rate) on 36 patients with hypersensitivity reactions (HSRs) to platinum chemotherapy (oxaliplatin, carboplatin or cisplatin) [9]. The intensity of the reactions for the included patients was reported as grade 2 for 61.1%, grade 3 for 25%, and grade 1 for 13.9% [9]. The initial infusion rate was 0.1 ml/h (0.01% of the total dose) for a timeframe of 15 min, and with increasing the infusion speed until 150 ml/h, the total dose of the drug was perfused in approximately 4 h. A recurrent HSR was reported in 83.4% of the perfusions, the vast majority being grade 1 - 51.7% and grade 2 - 44.8% [9], and the success rate of desensitization was 100% (175 procedures). The most frequent moment of the protocol when an HSR occurred was at the final step with 80 or 150 ml/h speed of infusion.

Li et al published their experience with 1 dilution desensitization protocol (4 steps of infusion rate) on 18 patients with mild or low-risk HSR [10]. The initial infusion rate was 50 ml/h (2.23% from the total dose of the drug) with a step of increasing the dose every 15 min to 150, 300, and 600 ml/h; the total timeframe was 1.5 h and 98.9% of the included patients succeeded to complete the protocol (95 procedures) [10].

Vidal et al on 12 studied patients concidering it more important to administer the same concentration of the drug (1 mg/ml) in different rates of infusion steps, every 15 min. The total duration of the process was 4.30 h and the rate of successful infusion was 100% (58 procedures) [11]. The initial rate of infusion was 0.1 ml/ h or higher (depending on the total dose, but with a total time constraint to be at the level of 4.30), with an initial administered dose of 0.01% of the total dose, in 16 steps.

Multiple dilutions and multiple steps

One important issue is represented by the initial dilution to be administered to the patient.

Which dose is safer to start in order not to prolong too much the desensitization process?

Starting dilution 1:10,000 or less

Syrigou et al started desensitization to 3 patients with an initial dilution of 1:100,000 which increased by 10-fold dilution by step (seven in total) with a previous premedication [12]. The exact dilution of the protocol was chosen after a skin prick test, and the rate of success was 100%.

Gastaminza et al in 8 of 11 included patients who received desensitization with a starting dilution of 1:10,0 d00 (5 dilutions in total, each with a 10-fold increase), the rate of success was 72% [13].

Kuo et al on 13 patients reported a rate of success of 84%, with a starting dilution of 1:10,000 or 1:100, depending on the number of 'steps' infusions with different concentration, until the final dose of chemotherapy drugs, twelve for first dilution, and five for subsequent dilutions [14].

Wong et al managed to administer all 200 cycles of desensitizations in 48 patients, with an initial dilution of 1:1,000,000 for those at very high risk, and 1:100 for low-risk and 1:1,000 for intermediate-risk [15].

Starting dilution 1:1,000

Madrigal-Burgaleta et al presented one of the most important institutional experiences with 192 patients who followed a desensitization protocol for ten years in this single institution [16], reporting 99,46% rate of success for 1027 rapid drug desensitization (RDD) protocol administration.

Altwerger et al on 129 included patients reported a succesfull rate of 96% (753 infusions without allergic reaction of 788 attempted) [6].

Bruchim et al reported that only 49 (89,1%) from initial 55 patients succeeded to follow the desensitization process for 207 RDD [17].

Kendirlinan et al included in their study 41 patients with allergic reaction to taxanes [22] and platin derivatives [17]. The initial dilution was different upon the type of chemotherapy, e.g. for taxanes it was 1:1,000 and 1:100 for platin derivatives, and the desensitization administration protocol was succesfull with a rate of 98,3% (122 cycles administered) [18].

Kang et al on 58 patients and 234 desensitization procedures revealed 5,2% of patients and 2,1% of procedures severe allergic reaction during classic protocol with initial dilution 1:1,000 [19].

Takase et al reported that on 20 patients and 79 RDD with initial dilution 1:1,000 the success rate was 95.2% and Confino-Cohen et al on 23 patients and 80 RDD published the same 95% positive result [20,21].

Starting dilution 1:100

Castells et al on 98 patients and 413 RDD had successful desensitization in 94% of the cases [22].

Wang et al reported 142 patients completed the desensitization procedures (574) [23]. Interestingly they considered it possible to rechallenge the chemotherapy administration without desensitization for those patients in which skin tests became negative.

Caiado et al showed that 11 (4%) of patients of 272 patients and 1471 RDD with serious reaction demanded epinephrine administration [24].

Regarding the starting dilution on published articles one mention needed to be made: the less diluted starting dose, the higher the risk for severe allergic reaction. Most of these protocols imposed that, at least the first infusion (if not all), should be administered in the intensive care unit (ICU). Of course, if the starting dose is low the total time for administration of the drug will be prolonged to several hours, which could limit their application to ambulatory patients. Increasing the rate of infusion instead could diminish the rate of success of the desensitization procedure. So it remains a difficult choice for oncologists to balance the risk and the benefits of one protocol over the other.

Stability of diluted solution of chemotherapy for desensitization procedures

As seen above, the strategy for desensitization presumes different dilutions for the start of the procedure. That could pose some questions regarding the technical possibility for the hospital's pharmacy to prepare the demanded dilution and the stability of the drug.

Data from published literature is limited and do not address all chemotherapy drugs.

Since all oncological chemotherapy agents are dissolved either in 0,9% sodium chloride solution or 5% glucose, Prat et al and Myers et al addressed this issue and showed that only a small fraction of carboplatin is affected (loss of <6% respectively <2%) and the solutions could be stable for a month at 25° Celsius [25,26].

Vasquez-Sanchez et al verified that small concentrations (0.2 and 0.02 mg/mL) of the drug (carboplatin), used as dilutions in almost all desensitization protocols are stable at room temperature, under protection from light [27]. Some changes are reported for 0.02 mg/mL dilution solution which is not proven to be stable for 24 h at room temperature.

Eiden et al confirmed the stability of another platin-derivative - oxaliplatin - at 0.2 and 1.3 mg/

dL for 14 days at a temperature of 4 and 20° Celsius [28].

In conclusion, our experience suggests that starting desensitization procedures at 1:1,000 dilution seems to be safe, with a very good rate of success (more than 97%), and does not increase the risk of a very severe allergic reaction. However, its treatment duration for 6 h per day could limit its application to hospitalized patients.

Acknowledgements

Knowledge transfer in clinical trials of biogenomics in oncology and related domains -BIOGENONCO, MySMIS Code: 105774, Financing contract No: 10/01.09.2016.

Conflict of interests

The authors declare no conflict of interests.

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