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ORIGINAL RESEARCH ARTICLE

The Healthcare Professionals' Perspective on Impact and Actions Taken Following Severe Infusion Reaction Events in Oncology Centers in Europe

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Abstract

Purpose The study aim was to describe the management strategies used for severe infusion-related reactions (SIRs) and understand the impact of such events in oncology day hospitals in France, Germany, Spain, and the UK.

Methods The study was based on qualitative telephone interviews and quantitative self-completion questionnaires and asked healthcare professionals about the impact of SIRs and consequent actions taken.

Results The procedures to prevent and manage SIRs were similar across countries and settings. In all countries, they were part of a larger risk-assessment and adverse events-prevention process. Preventive measures included patient history, risk assessment, pre-medication, and close monitoring of high-risk patients. The management procedures comprised stopping the infusion, triggering of the emergency chain, administering corticosteroids ± antihistamines, and hospitalization if necessary. The recalled SIRs had important consequences to affected patients, healthcare providers, and hospital organizational plans. All affected patients needed to be monitored closely for a prolonged time, thus blocking hospital beds. 44% of patients needed to be hospitalized, 17% needed resuscitation, and one patient died of cardiac arrest immediately after the start of the infusion. Importantly, 82% of patients were not re-challenged with the presumedly SIR-causing regimen or re-challenged in a later line.

Conclusion SIRs are unpredictable in nature, may have an extremely rapid onset, and are potentially fatal. Such events have a profound impact on the affected and surrounding patients, the care team and the organizational plan of the day-hospitals. Specific tools to reliably identify high-risk patients and predict the occurrence of events are needed.

Key Points

Severe infusion reactions are unpredictable in nature, may have an extremely rapid onset, and are potentially fatal. They have a profound impact on the affected and surrounding patients, the care team, and the organization of the day-hospitals.

Although procedures to prevent and manage severe infusion reactions are well established and homogeneous across the study countries, there is room for improvement.

New tools to reliably identify patients at high risk of developing severe infusion reactions and predict their occurrence would be highly appreciated by the practitioners to reduce the risk of fatal outcomes.

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1 Introduction

Infusion reactions are disorders characterized by adverse reactions to the infusion of pharmacological or biological substances, such as cytotoxic agents or monoclonal antibodies [1, 2]. They are defined as "non-dose related, unpredictable, generally unrelated to the drug's pharmacological activity and they usually resolve when treatment is terminated" [3–5]. These reactions may be experienced immediately (i.e., during the infusion or within the 1–6 h after the last administration), or with a delay (i.e., within hours or days after an infusion) [2]. Infusion reactions can be categorized as either allergic reactions, i.e., an immunoglobulin E (IgE)-driven antibody reaction, or IgE-independent (anaphylactoid) [2, 6, 7]. The clinical manifestations are similar regardless of the underlying cause and include mucocutaneous, respiratory, circulatory, and abdominal symptoms, and are sometimes life-threatening [2]. The incidence of severe infusion reactions (SIRs; defined as infusion reactions of grades 3–5) in systemic therapies varies across the different classes of antineoplastic agents and within a given class, and ranges between < 1% and ~ 30% [2, 6]. In chimeric monoclonal antibody therapies (cetuximab, rituximab), SIR incidence was reported to range between 2–5% (cetuximab) and 10% (rituximab) [2]. In humanized (trastuzumab, bevacizumab) or fully human (panitumumab) monoclonal antibodies, SIR incidence was < 1% [2]. Differences in the glycosylation patterns resulting from mammalian cell lines producing chimeric versus humanized or fully human antibodies may influence recognition by innate immune cells [8, 9].

There is only a small body of literature on infusion reactions. Reports of SIR incidence in real-life clinical practice show a mixed picture, with some reports finding a higher incidence in observational studies compared to controlled clinical trials [10, 11] and other studies suggesting a lower incidence in real-life [12]. Geographical differences were also noted [11]. Within the medical literature, no uniform definition is used to describe infusion reactions [13], and vast under-reporting of hypersensitivity reactions and lack of correct diagnosis in real-life have been documented [14]. The inconsistent definition and reporting practices cloud the importance of SIRs in clinical practice and hamper research in this area. To resolve this, several international bodies have attempted to standardize the nomenclature of allergy, which now forms the basis of the European Society of Medical Oncology (ESMO) guidelines on the management of infusion reactions, including ways to properly document SIRs in clinical practice [2].

There is currently limited literature on the management of SIRs and their impact on clinical regulations and procedures within European oncology centers. A single study demonstrated substantial resource use, staff stress and patient anxiety [15]. The objectives of the present mixed-methods study were to understand the current procedures to prevent and manage SIRs in oncology day-hospitals across four European countries to describe the impact of past events on safety procedures, the role of key stakeholders, their level of awareness of associated risks, and their experiences with such events.

2 Methods

2.1 Study Design

The research follows a hybrid methodology, combining a quantitative component with a questionnaire completed prior to a telephone in-depth interview (qualitative component) among the same respondents. It was conducted in France, Germany, Spain, and the UK among oncology healthcare providers (HCPs, i.e., head nurse, oncologist, pharmacist, safety manager, risk manager, pharmacovigilance manager, quality manager, medical information manager within oncology centers). In Germany, oncologists' offices were included to reflect the specifics of the local oncology management. The data collection period was January 2018 to April 2018.

2.2 Eligibility Criteria

Centers were randomly selected from national sampling lists of outpatient centers to ensure representativeness by institutional size, type, and region (see Table S1 in the Online Supplemental Material for regions included). Centers were included if they treated ≥ 20 cancer patients per day and had experienced at least one severe, i.e., grades 3–5, infusion reaction event within the last 5 years prior to study start. HCPs were eligible if they had ≥ 5 years of clinical experience and had spent ≥ 2 years at the respective center.

2.3 Quantitative Analysis

The questionnaires were self-completed and returned prior to the interview. They included information on the characteristics of the respective center environment and a description of the infusion pathway from risk assessment to infusion monitoring. The analysis of the quantitative component was undertaken by Kantar Health using Qlikview software version 11.20.12904.0 SR12 developed by QlikTech (Pennsylvania, USA). Due to the nature of the study, the analysis is only descriptive. Any categorical variables (when available) were summarized using frequency and percentage. Continuous data have been presented with the mean, median, minimum, and maximum.

2.4 Qualitative Analysis

All telephone interviews were audio-recorded with permission. HCPs were asked 25 questions covering processes to prevent and manage SIRs in the respective HCPs clinic. HCPs were also asked to recall the most striking case of SIR (grade 3 or 4) that had occurred during the past 5 years and to spontaneously describe patient characteristics, agents received, SIR symptoms observed, steps taken to manage the SIR, and outcome on patient, staff, and hospital processes.

No computer-assisted qualitative data analysis software (CAQDAS) was used in this process – only transcripts, audio-recording and content-analysis grid. Data were analyzed based on grounded theory method. Data were coded in terms of basic psycho-social processes, based on how participants acted in response to different contexts. Verbatim quotes were reported at the final stage to illustrate the analysis with the unfiltered wording of the participants. The selection criteria for the verbatim quotes were based on their relevance and ability of the quotation to summarize the view of the majority and the opposite view when relevant.

A detailed description of questionnaires and interviews is provided in the Online Supplemental Material.

3 Results

3.1 Characteristics of Centers and Practitioners

In total, 194 HCPs were contacted and 71 from 46 centers accepted to be interviewed (Fig. S1). In Germany, one HCP did not complete the self-completion questionnaire but participated in the telephone interview. Of the 70 HCPs, 47% were oncologists, 39% were head nurses, and 14% were pharmacists. While all respondents had ≥ 5 years of experience in their role as per inclusion criteria, 90% had worked ≥ 5 years in their current hospital. Overall, 53% worked at university or teaching hospitals; 49% worked at centers with 200–499 beds. The most frequently treated tumor types were breast, lung, and colorectal cancer. On average, 52 infusions were administered to cancer patients per day (median 40; range 4–150). Supplemental Tables S2A and S2B show the center and HCP characteristics, respectively.

3.2 Description of Stakeholders' Roles

The role of the participating HCPs was very similar in all countries: they all worked in day-hospitals, as per the selection criteria.

The responsibilities of head nurses included management of chemotherapy specialist nurses, involvement in direct patient care including patient education, management of treatment administration and monitoring, and attending to organizational tasks linked to patient management. Of the 27 head nurses, eight (30%) had additional higher level responsibilities. In France, 2 out of 9 head nurses had a role in human resources, training staff and liaising between the patients and the physicians. In Germany, 1 out of 6 head nurses had more time dedicated to nurse staff education and training. In Spain, 2 out of 5 head nurses were involved in organization and operations and liaised with oncologists and the hospital pharmacy. In the UK, 3 out of 7 head nurses managed nurse-led clinics and were authorized to prescribe chemotherapy.

In all countries, oncologists stated that they were dedicating ≥ 80% of their time to patient care. Their roles included making and subsequently explaining the patient diagnosis, discussing their cases at the tumor boards, planning the therapeutic strategy in close discussion with the patient, and prescribing and validating the chosen regimen. All oncologists were involved in managing SIRs, although they were not the first witnesses.

In all countries, the safety managers involved in the prevention process of SIRs were pharmacists. They were responsible for the validation and preparation of chemotherapy drugs and for screening the prescriptions to ensure the treatment protocol was being adhered to.

3.3 Awareness of Signs of Severe Infusion-Related Reactions (SIRs)

Generally, the warning signs of SIRs (Fig. 1), as questioned during the qualitative interview, were described similarly by all respondents but each stakeholder typically witnessed different stages. It was noted, however, that SIRs did not always show clear warning signs and could present with sudden anaphylaxis or loss of consciousness. For all respondents the unpredictable and emergency nature of SIRs was considered the most challenging aspect, especially the possibility of a fatal outcome.

> "…A serious infusion reaction is not difficult to spot. It's quite sudden, it's quite pronounced…you will get agitation with the patient, red face, short of breath, may complain of chest pain. You can't miss that!" (Nurse, Teaching Hospital, UK)
>
> "Rash, difficulty breathing, nausea, dizziness, fever… the warning signs are very clear." (Head Nurse, University Hospital, Spain)
>
> "Breathing problems, like rapid breathing, their lips turning blue…their oxygen saturation may be less than 90%, confused patients…patient may be pale or have low blood pressure, feeling faint or drowsy. Those are the kind of things we look for." (Safety Manager, Teaching Hospital, UK)

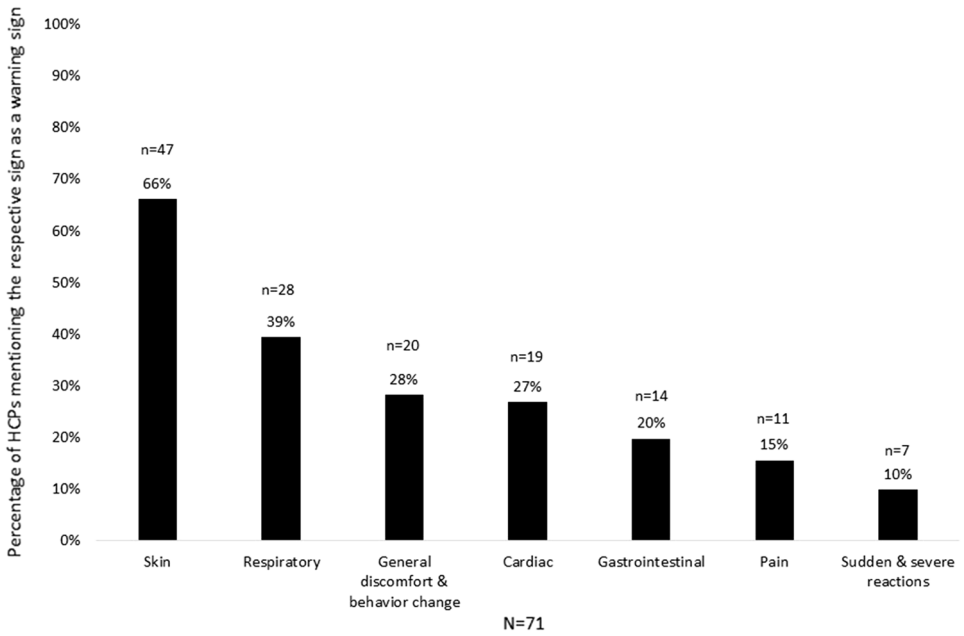

Fig. 1 Recall of infusion reaction warning signs. Percentages represent the proportion of respondents out of 71 who listed the respective sign. Skin: Flushing, urticaria, rashes, swelling, pruritus, sweat, lips changing color, hand erythema, angioedema, tingling sensation. Respiratory: Dyspnea, breathing difficulty, low oxygen saturation, bronchospasm, cough, laryngeal edema. General discomfort and behavior change: Faint, dizzy, headache, fear, confusion, agitation, hypothermia, hyperthermia, apathy, restlessness. Cardiac: Tachycardia, low blood pressure, angina. Gastrointestinal: Nausea, vomiting. Pain: Back pain, lower back pain, stomach pain, chest pain. Sudden and severe reactions: Drop in vital signs, anaphylaxis, loss of consciousness, severe chest pain

3.4 Processes to Prevent SIRs

Overall, 59% of the 70 HCPs reported that risk-assessment routines for SIRs were systematically considered and were more frequently considered if there was a history of allergies (74%) or infusion reactions (73%; Table 1; assessed in quantitative questionnaire). Risk assessment for SIRs is typically part of the oncologist-led full patient assessment to determine eligibility for the selected systemic treatment. In general, such risk assessment consists of the following criteria: (a) type of anticancer therapy (especially when monoclonal antibodies, taxanes, or platinum salts are considered), (b) patient history (including earlier and/or minor allergic episodes or infusion reactions), and (c) relevant co-morbidities, general fitness, and treatment contraindications. These criteria were considered sufficient to identify patients at high risk of developing SIRs, but they do not allow an accurate prediction of the occurrence of actual events. Prior to infusion, the nurses inform the patients about warning signs and advise them to be vigilant.

Risk assessment and patient information were not formalized as a documented procedure due to the unpredictable nature of SIRs. In all countries, steps to prevent SIRs are based on a mix of local/hospital (73%), national (26%), and international (14%) guidelines, and form part of hospital/center standard operating procedures (Supplemental Table S3, qualitative interview).

3.5 Premedication to Prevent SIRs

Premedication to prevent SIRs, along with other types of premedication such as anti-emetics or growth factors, are generally included in the electronic prescription mechanism as part of the protocol for systemic regimens. Premedication with corticosteroids was systematically considered according to 59% of respondents and premedication with antihistamines according to 51% (Table 2; quantitative questionnaire and quantitative interview). Premedication protocols follow the label recommendations of the respective anticancer agents. For patients who are re-challenged after experiencing SIRs in earlier cycles, hypersensitivity protocols are followed. The premedication protocol is typically validated by the pharmacist.

> "The premedication is included in the chemotherapy software so when the physician enters the chemotherapy, the premedication appears automatically, it is printed out on a sheet and supplied with the chemo drug." (Nurse, Public General Hospital, France)

Table 1 Infusion reaction-related aspects considered in the risk assessment

Category	Total ($N=70$)	France ($N=20$)	Germany ($N=16$)	Spain ($N=20$)	UK ($N=14$)
Patient characteristics (age, sex status, co-morbidities, history), *n* (%)					
Systematically considered	41 (59)	15 (75)	10 (63)	9 (45)	7 (50)
Frequently considered	13 (19)	3 (15)	2 (13)	4 (20)	4 (29)
Occasionally considered	2 (3)	0 (0)	0 (0)	2 (10)	0 (0)
Only considered for some agents/classes	13 (19)	2 (10)	3 (19)	5 (25)	3 (21)
Immunotherapies	2 (3)	2 (10)	0 (0)	0 (0)	0 (0)
Monoclonal antibodies	11 (16)	0 (0)	3 (19)	5 (25)	3 (21)
Platinum salts	11 (16)	2 (10)	1 (6)	5 (25)	3 (21)
Taxanes	13 (19)	2 (10)	3 (19)	5 (25)	3 (21)
Other chemotherapy	2 (3)	0 (0)	0 (0)	0 (0)	2 (14)
Rarely considered	1 (1)	0 (0)	1 (6)	0 (0)	0 (0)
Specific history of infusion reactions, *n* (%)					
Systematically considered	51 (73)	18 (90)	7 (44)	17 (85)	9 (64)
Frequently considered	12 (17)	1 (5)	7 (44)	1 (5)	3 (21)
Occasionally considered	2 (3)	0 (0)	1 (6)	0 (0)	1 (7)
Only considered for some agents/classes	5 (7)	1 (5)	1 (6)	2 (10)	1 (7)
Monoclonal antibodies	5 (7)	1 (5)	1 (6)	2 (10)	1 (7)
Platinum salts	2 (3)	0 (0)	0 (0)	2 (10)	0 (0)
Taxanes	5 (7)	1 (5)	1 (6)	2 (10)	1 (7)
Other chemotherapy	1 (1)	1 (5)	0 (0)	0 (0)	0 (0)
Specific history of allergies, *n* (%)					
Systematically considered	52 (74)	18 (90)	11 (69)	14 (70)	9 (64)
Frequently considered	8 (11)	1 (5)	3 (19)	0 (0)	4 (29)
Occasionally considered	5 (7)	0 (0)	1 (6)	3 (15)	1 (7)
Only considered for some agents/classes	4 (6)	1 (5)	0 (0)	3 (15)	0 (0)
Monoclonal antibodies	4 (6)	1 (5)	0 (0)	3 (15)	0 (0)
Platinum salts	4 (6)	0 (0)	0 (0)	3 (15)	1 (7)
Taxanes	5 (7)	1 (5)	0 (0)	3 (15)	1 (7)
Other chemotherapy	3 (4)	1 (5)	0 (0)	2 (10)	0 (0)
Rarely considered	1 (1)	0 (0)	1 (6)	0 (0)	0 (0)
According to the administration position in the cycle (first, second, eighth, etc.), *n* (%)					
Systematically considered	44 (63)	13 (65)	13 (81)	10 (50)	8 (57)
Frequently considered	7 (10)	2 (10)	0 (0)	1 (5)	4 (29)
Occasionally considered	12 (17)	5 (25)	2 (13)	4 (20)	1 (7)
Rarely considered	2 (3)	0 (0)	0 (0)	2 (10)	0 (0)
Never considered	5 (7)	0 (0)	1 (6)	3 (15)	1 (7)

"We have those medications already pre-prescribed on our chemotherapy charts. We're fully electronic in terms of chemotherapy prescription. It's more down to the regimes themselves. For a taxane regime or something like bleomycin…those pre-medications are already pre-populated within the chart, so it doesn't have to be actively prescribed, so they are there for a routine administration for the nursing staff, so all patients will get an antihistamine and a dose of steroid…" (Oncologist, Teaching Hospital, UK)

3.6 Monitoring for SIRs

In all countries, nurses were responsible for patient monitoring. Typically, monitoring consists of visual observation, direct verbal interaction, and the measurement of vital signs, such as blood pressure, pulse, respiratory rate, temperature, and oxygen saturation, prior to, during, and after the infusion. The frequency of observation followed the monitoring guidelines within the protocols for each regimen, but

Table 2 Premedication to prevent infusion reactions

Category	Total ($N=70$)	France ($N=20$)	Germany ($N=16$)	Spain ($N=20$)	UK ($N=14$)
Corticosteroids, *n* (%)					
Systematically considered	41 (59)	10 (50)	14 (88)	11 (55)	6 (43)
Frequently considered	9 (13)	5 (25)	0 (0)	2 (10)	2 (14)
Occasionally considered	5 (7)	0 (0)	0 (0)	0 (0)	5 (36)
Only considered for some agents/classes	17 (24)	5 (25)	2 (13)	7 (35)	3 (21)
Monoclonal antibodies	14 (20)	4 (20)	2 (13)	6 (30)	2 (14)
Platinum salts	10 (14)	2 (10)	0 (0)	6 (30)	2 (14)
Taxanes	14 (20)	5 (25)	2 (13)	6 (30)	1 (7)
Other chemotherapy	3 (4)	2 (10)	0 (0)	0 (0)	1 (7)
Antihistamines, *n* (%)					
Systematically considered	36 (51)	9 (45)	9 (56)	9 (45)	9 (64)
Frequently considered	10 (14)	4 (20)	2 (13)	3 (15)	1 (7)
Occasionally considered	8 (11)	3 (15)	3 (19)	0 (0)	2 (14)
Only considered for some agents/classes	15 (21)	4 (20)	2 (13)	8 (40)	1 (7)
Monoclonal antibodies	17 (24)	4 (20)	2 (13)	8 (40)	3 (21)
Platinum salts	9 (13)	2 (10)	0 (0)	7 (35)	0 (0)
Taxanes	13 (19)	3 (15)	2 (13)	8 (40)	0 (0)
Other chemotherapy	1 (1)	1 (5)	0 (0)	0 (0)	0 (0)
Rarely considered	1 (1)	0 (0)	0 (0)	0 (0)	1 (7)
Other premedication, *n* (%)					
Antipyretic agent	2 (3)	2 (10)	0 (0)	0 (0)	0 (0)
Paracetamol	3 (4)	2 (10)	0 (0)	1 (5)	0 (0)

For this study a structured questionnaire was used that enquired about premedication procedures in a multiple-choice manner but allowed for free text to provide other procedures not included in the predefined answers to obtain objective quantitative information but at the same time to allow for items not included within the structured questionnaire. Despite this it is possible that information may not have been reported within the free text

typically they were recorded in 15- to 30-min intervals, with shorter intervals in the first hour. Overall, 54% of the 70 respondents reported monitoring patients during the entire administration time and in all cycles, and 32% reported monitoring during the entire infusion in selected cycles (SIR monitoring information was collected through qualitative and quantitative work; Table 3 summarizes quantitative work).

High-risk patients were handled with elevated vigilance. The responsibility for high-risk patients could be split among the nursing team to spread the risk, and some centers allocated them specifically to more experienced nurses. Infusion administration was done in chairs with an oxygen point and in direct line of vision of attending staff, i.e., front row chair or room in direct view, and was usually planned earlier in the day to ensure physicians were available. Frequent observations were scheduled, especially during the first infusion; occasionally, nurses remained with the patient for the first 30 min. Such patients were also monitored for delayed reactions. Optionally, infusions were administered in an inpatient setting in case of re-challenge of a patient with known previous SIRs.

"At our place and in many other places it is handled like that: The patient is sitting close, so that we can see him and check on him regularly; we also document blood pressure and pulse regularly; during the infusion, the vital parameters are measured." (Oncologist, office-based, Germany)

"It's observing the patient and measuring vital observations, baseline, after and during the treatment… includes temperature, pulse blood pressure and oxygen saturation…if it is a half hour or more infusion, they will usually get it done at 15-min intervals…if it is a very long infusion, it may be every half hour or hour…" (Oncologist, Teaching Hospital, UK)

"In case of high-risk patients, monitoring is more intensive, e.g., you have a look at the patient every few minutes." (Oncologist, office-based, Germany)

3.7 Procedures to Manage SIRs

Processes to manage SIRs follow similar steps in all countries and across all settings. The sequence of actions and the distribution of responsibilities between the different stakeholders is laid out in Fig. 2. The main difference

Table 3 Monitoring strategies during infusion

Category	Total ($N=70$)	France ($N=20$)	Germany ($N=16$)	Spain ($N=20$)	UK ($N=14$)
Monitoring over the entire administration time for all administration cycles, *n* (%)					
Systematically considered	38 (54)	13 (65)	8 (50)	9 (45)	8 (57)
Frequently considered	15 (21)	5 (25)	2 (13)	4 (20)	4 (29)
Occasionally considered	4 (6)	1 (5)	1 (6)	1 (5)	1 (7)
Only considered for some agents/classes	10 (14)	1 (5)	2 (13)	4 (20)	3 (21)
Monoclonal antibodies	9 (13)	1 (5)	2 (13)	4 (20)	2 (14)
Platinum salts	5 (7)	0 (0)	0 (0)	4 (20)	1 (7)
Taxanes	6 (9)	1 (5)	1 (6)	4 (20)	0 (0)
Rarely considered	4 (6)	0 (0)	2 (13)	2 (10)	0 (0)
Unspecified	1 (1)	0 (0)	1 (6)	0 (0)	0 (0)
Monitoring over the entire administration time for selected cycles only, *n* (%)					
Systematically considered	10 (32)	4 (57)	1 (14)	2 (18)	3 (50)
Frequently considered	12 (39)	2 (29)	3 (43)	5 (46)	2 (33)
Occasionally considered	4 (13)	0 (0)	2 (29)	2 (18)	0 (0)
Only considered for some agents/classes	4 (13)	1 (14)	0 (0)	2 (18)	1 (17)
Monoclonal antibodies	4 (13)	1 (14)	0 (0)	2 (18)	1 (17)
Platinum salts	3 (10)	0 (0)	0 (0)	2 (18)	1 (17)
Taxanes	3 (10)	1 (14)	0 (0)	2 (18)	0 (0)
Never considered	1 (3)	0 (0)	1 (14)	0 (0)	0 (0)
Monitoring during the first hour of administration of all cycles, *n* (%)					
Systematically considered	9 (43)	2 (67)	2 (33)	4 (44)	1 (33)
Frequently considered	4 (19)	0 (0)	1 (17)	2 (22)	1 (33)
Occasionally considered	3 (14)	0 (0)	2 (33)	1 (11)	0 (0)
Only considered for some agents/classes	4 (19)	1 (33)	1 (17)	1 (11)	1 (33)
Monoclonal antibodies	5 (24)	2 (67)	1 (17)	1 (11)	1 (33)
Platinum salts	1 (5)	0 (0)	0 (0)	1 (11)	0 (0)
Taxanes	3 (14)	1 (33)	0 (0)	1 (11)	1 (33)
Rarely considered	1 (5)	0 (0)	0 (0)	1 (11)	0 (0)
Monitoring during the first hour of administration for selected cycles only, *n* (%)					
Systematically considered	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)
Frequently considered	3 (25)	0 (0)	1 (25)	1 (20)	1 (50)
Occasionally considered	2 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Only considered for some agents/classes	6 (50)	1 (100)	1 (25)	3 (60)	1 (50)
Monoclonal antibodies	5 (42)	1 (100)	1 (25)	3 (60)	0 (0)
Platinum salts	3 (25)	0 (0)	0 (0)	3 (60)	0 (0)
Taxanes	4 (33)	0 (0)	0 (0)	3 (60)	1 (50)

between severe (grades 3–5) versus non-severe events is the speed of escalation, determining crash team involvement, and patient admission to inpatient care. After the SIR event, re-challenging is individually reconsidered in patients with an event up to grade 3. In the UK and Spain, desensitization might also be considered. When the reaction is very severe (grade 4), the patient is not re-challenged with the same product in any country.

"Grade 4 is anaphylaxis, so that's a medical emergency, so a crash team composed of intensivists and highly trained nurses are called for as the patient is likely to require hospital admission and more supportive measures." (Oncologist, Cancer Centre, UK)
"The infusion must be stopped immediately, then – there are always two nurses – one of us calls the physician in charge if he is present, or the ICU physi-

cian. But it all depends on the grade of the reaction. I have never witnessed a severe reaction so calling the referring physician is much easier because he knows the patient's history, and most of the time an infusion of hydrocortisone or Solumedrol and a little bit of oxygen are sufficient." (Nurse, private hospital, France)

"When I call in an emergency, we are three plus the doctor; one stays with the patient together with the doctor, the other one prepares the medication; and the third nurse is responsible for the phone, just in case the emergency doctor has to be called, or if we need something that is not at hand." (Nurse, hospital-based, Germany)

3.8 Staff Education and Adherence to the Procedures

Education on SIRs typically forms part of a larger sequence of staff training primarily conducted by head nurses. The responsibility of ensuring protocol compliance was often shared between physicians, health executives, and the quality department (Supplemental Table S4). In France and the UK, compliance audits are carried out. However, these audits do not necessarily occur after an event.

"There's an emergency training once a year, where we train for such a situation; we work hand in hand." (Nurse, office-based, Germany)

3.9 Description of Recalled SIR Events

HCPs were asked to spontaneously recall the most striking case of SIR that occurred in their practice and to describe its characteristics and measures taken to manage the event (Table 4). In 17% of 71 recalled cases, the patients needed resuscitation or a crash cart, and in 44%, affected patients were admitted to the oncology or intensive care unit. There is one account of a patient who died of cardiac arrest immediately after the start of the infusion. A corticosteroid and/or antihistamine were administered to the patient according to 82% of recalls. In 82% of cases the SIR led to termination of the current anticancer regimen and patients were not or not immediately re-challenged. Even in optimally managed acute response, a long-term negative impact of the SIR was reported: One patient needed to be switched to palliative care and another moved to another country to take part in a clinical trial not available at home.

SIR events were considered an occasion to reassess existing procedures and discuss needs for improvement. Inadequacies were mostly structural, such as the floor layout and center organization. Examples mentioned were an insufficient number of chairs for all high-risk patients in direct visual contact with the nurses, or the oncologists on duty were located too far away to arrive promptly in case of emergency. High staff turnover poses a risk as nurses with less experience in procedures and center facilities would be responsible for managing such events. Finally, the number of available staff was perceived as insufficient. Reported best practice changes were not formalized and decided at a nurse

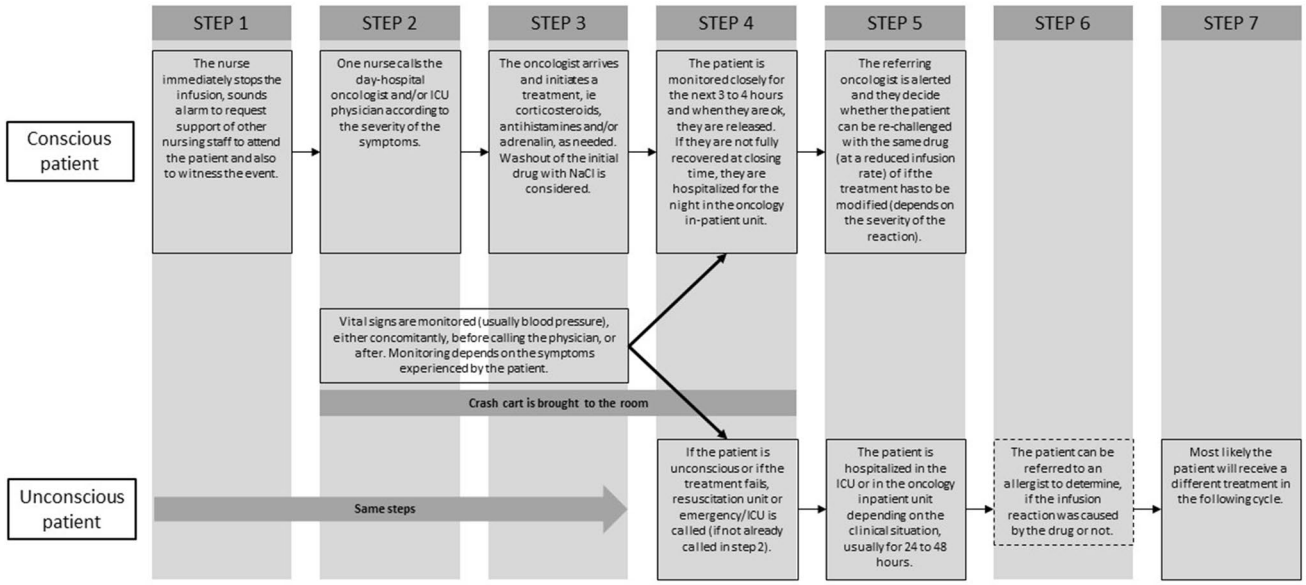

Fig. 2 Description of the infusion reaction management process. *Chemo* chemotherapy, *Hosp* hospital, *NaCl* sodium chloride solution, *ICU* intensive care unit, *IV* infusion. Note: This figure provides an overview of the process as articulated by the healthcare professionals during the telephone interviews and it is a summary based on all healthcare professionals' comments

Table 4 Spontaneous recount of actions taken during healthcare provider-recalled severe infusion-related reaction event—in chronological order of events

Action taken, *n* (%)	(*N* = 71)
Stopped the infusion immediately	65 (92)
Called the oncologist	40 (56)
Called the ICU physician	13 (18)
Monitored vital signs	71 (100)
Administered a corticosteroid ± antihistamines	58 (82)
Monitored the patient for 3–4 h	71 (100)
(Immediate) treatment re-challenge[a]	13 (18)
Needed resuscitation/crash etc	12 (17)
Patient was hospitalized in oncology unit or ICU	31 (44)

ICU intensive care unit

[a]This category combines immediate re-challenge with the agent that presumably caused the severe infusion-related reaction in the same treatment line and re-challenge in a later treatment line

level. However, the HCPs stated a high level of personal satisfaction about the established procedures for both prevention and management of SIRs.

The HCPs responded that the resolution of SIR events involves all available nurses and doctors and disrupts the organization, as all planned activities for the day need to be stopped immediately and can only be resumed after resolution. SIRs can thus be stressful for staff and other patients who witness the situation and whose care is interrupted or delayed.

The nursing staff as direct witnesses were practically and emotionally more affected than oncologists and pharmacists/safety managers who arrived later or were not directly involved, respectively.

> "They are scary, the patient can die…but everything has a protocol, everybody knows what they need to do." (Head Nurse, University Hospital, Spain)
> "Everyone, including me, is shocked that such severe reactions occur; we were particularly shocked, because they occur very rarely, and when you face such a situation, you are extra upset and shocked. And afterwards, you are happy that everything worked out fine." (Oncologist, office-based, Germany)

Despite the issues mentioned, HCPs expressed high levels of satisfaction with the prevention process (median score of 4 out of 5) and management (median score 4 out of 5) of their institutions.

3.10 Improvements to Current Practices

When asked, the respondents proposed measures to improve workflows and hospital organization, staff and patient education, risk assessment, and patient monitoring, and to enable a more rapid and adequate emergency response.

The efficiency of SIR prevention and/or management may be hampered by punctual dysfunctions, such as changes in the routine organization of the day-hospital center (new staff, difficulty getting hold of the physician, staff shortage due to holidays) or to the actual structure of the center (nurse station not in direct visual field of the patient, no place to rapidly isolate the patient or to easily access the crash cart). Therefore, the organizational structure and floor layout are crucial, i.e., direct visual contact between nurses and patients, sufficient number of chairs with oxygen access, rapid patient isolation, and easy access to the crash cart. Infusion administration should be scheduled at times of peak staff presence, especially physicians. An organizational re-assessment should involve the allergy unit and focus on sensitization. An improved prescription software should feature mandatory pre-infusion checklists showing a detailed history of previous allergic reactions and preventing chemotherapy administration until all risk assessment criteria have been covered, and alerting when a drug has previously caused an SIR.

> "The traceability could be improved in our software, in our EMRs, the traceability of allergies, of the patient's history. It's something that is missing. I think that physicians systematically ask questions about the patient's history, everything is recorded in the reports, etc., but ergonomically speaking, we have to look at all the reports to see if there were any warnings for some molecules, so it would be great if we had alerts." (Safety Manager, Cancer Center, France).

Nurse training on new products to increase personal awareness and improve patient education should include minor and major SIR warning signs, drug–drug interactions, and dietary supplements and herbal products. Better tools for the identification of high-risk patients, including predictive biomarkers, alternative treatments with lower risk of SIRs, more efficacious and safer premedication, and an improved, tailored desensitization protocol are needed.

Post-event, more time should be devoted to full root-cause analysis and debrief. National databases to document events and share data analyses were also proposed. National guidelines should be updated, and hospital standard operating procedures aligned accordingly, including benchmarking efforts and internal audits. Product manufacturers should be involved in the discussions post-event.

4 Discussion

SIRs are severe adverse events potentially involving anaphylaxis and death. SIRs are unpredictable, and a patient can experience an event after having undergone several treatment cycles with the same agent and without showing any

warning signs. As a general rule: The more rapid the onset, the more severe the infusion reaction [2, 16]. Therefore, SIRs require constant monitoring, the recognition of early warning signs, if any, and immediate reaction of all available staff as soon as the first symptoms appear, to avoid escalation of severity.

The recalled 71 SIR events had important consequences for the affected patients (i.e., requiring hospitalization or resuscitation), the HCPs, and organizational plans of the hospitals. One patient died of cardiac arrest immediately after the start of the infusion. All patients needed to be monitored closely for a prolonged time, thus blocking hospital beds. In 82% of recalls, affected patients were not re-challenged with the presumedly SIR-causing regimen or re-challenged in a later line. The decision to restart the treatment depends on the nature and severity of the SIR. Desensitization protocols are available for limited use in experienced centers. These are not always effective, often have no permanent effect, and may need to be repeated prior to every cycle [2, 17]. In case of grade 3 or 4 SIRs or in true anaphylaxis, re-challenge should not be attempted according to the ESMO guidelines [2]. The decision not to continue the previous treatment is especially deleterious for patients who already have undergone several prior lines and may run out of options. In fact, one patient needed to be switched to palliative care and another moved to another country to take part in a clinical trial not available at home. Although HCPs felt they were well trained on emergency procedures and perceived the available protocols as useful under conditions of stress, such events had an emotional impact. This was consistent with a survey conducted among oncology nurses, where close to 80% described a "tremendous amount of stress and anxiety to the entire staff" [18].

This survey also included a more detailed assessment of the emotional impact of SIRs on affected and surrounding patients, an aspect that was not assessed in detail in the present study. According to this survey, almost all nurses reported that SIRs increased anxiety among affected and surrounding patients (~78%), took infusion time away from other patients (~98%), and created a chemotherapy backlog (~75%) [18].

It needs to be noted that the findings on the reactions of HCPs to the occurrence of SIRs may be impacted by the degree to which first responders are authorized to actively manage the SIR, if they are authorized to start the process of treating the SIR or if management is delayed until a trained nurse or a qualified physician arrives or is reached to guide the response. The respective level of authorization may vary by site and in different legislations [19, 20].

Established protocols to prevent and manage SIRs are aligned with national and international guidelines. They strongly focus on preventing the escalation of an infusion reaction to a severe stage. There is a standardized risk assessment to identify patients potentially at high risk of infusion reactions. Systematic administration of corticosteroids (according to 59% of respondents) and antihistamines (51%) was conducted as part of the general premedication protocols for the anticancer regimens in larger centers but followed more individualized approaches in smaller centers. To avoid escalation of the infusion reaction to a severe stage, close monitoring of the patients to detect early warning signs are standard. Overall, 54% of respondents monitored patients during the entire administration time and in all cycles. High-risk patients undergo especially close-interval monitoring and use chairs with oxygen supply and in line of sight of the nurses' station. These protocols guide HCPs on every step of preventing and handling the emergency, and HCPs consistently reported that they personally felt well equipped and trained to handle the situation. However, it needs to be noted that measures of satisfaction with the processes are based on the HCPs' personal assessment for their own education and institutions and were not derived from a formalized assessment of the quality of local procedures with respect to international guidelines.

The following study limitations should be noted. A mixed-methods study design approach was used. The qualitative interviews included a subjective element; however, open-ended questions were chosen to allow a deeper understanding of the procedures and their rationale. SIR events and their impact were documented as recalled by the HCPs and were not derived from patient files. This also implies that no clear delineation of the types of agents with the types of reactions is possible from recall; therefore, some recall bias may have been introduced. The recruiting criteria included participants who had experienced an SIR in the last 5 years to minimize recall bias and to allow time to describe any subsequent changes in procedures. However, recruitment of nurses focused on head nurses, who typically have a managerial role rather than administering antineoplastic agents on a daily basis. However, only eight of 27 participating nurses had a higher level of responsibility such as human resources, staff training, and management. To ensure the validity of their reports, participating nurses must personally have experienced an SIR to participate in the study. Importantly, the management of infusion reactions may have been different between nurses who were authorized to respond directly compared to those who needed to wait for qualified HCPs to initiate the first response. The recruitment process in Germany requiring authorization from the hospital manager led to many refusals, resulting in an over-representation of office-based practitioners. However, the level of homogeneity of the responses across countries and across settings suggests that the impact is minimal. The present assessment included outpatient hospitals only. The survey of Colwell and colleagues, however, reported substantial

differences between inpatient and outpatient hospitals in the way SIRs were handled and followed-up [18]. For this study a structured questionnaire was used that enquired about premedication procedures in a multiple-choice manner but allowed for free text to provide other procedures not included in the pre-defined answers in order to obtain objective quantitative information, but at the same time to allow for items not included within the structured questionnaire. Despite this, it is possible that information may not have been reported within the free text.

The measures proposed by HCPs to improve the processes governing the prevention and management of SIRs should be subject to further debate and validation and may enrich future international knowledge exchange efforts and guidelines. Proposed measures were: (a) an improved prescription software, featuring mandatory pre-infusion checklists and a warning in case of documented previous allergic reactions, with improved identification of patients at high risk of developing SIRs, such as predictive biomarkers; (b) the establishment of an international database of documented SIR events including data analysis; (c) educational efforts to better understand treatments and their potential to produce SIRs. Taken together, such efforts could substantially improve the scientific knowledge base on the incidence of SIRs, the circumstances of their occurrence, and their best management, and could thus be synthesized to inform future international guidelines.

This study raises some important questions to be addressed in future research, such as estimating the rate of SIRs overall and on a center level; estimating the impact of the level of authorization of the nurses to respond to the SIRs in legislations where they can immediately respond on a nurse level compared to legislations where they have to wait for doctors' instructions. Importantly, the proposed measures for improvement of current processes captured within this study need to be further explored in a systematic way as part of future research that could potentially form the basis for updating current processes and guidelines.

5 Conclusion

SIRs are unpredictable in nature, may have an extremely rapid onset, and are potentially fatal. Such events have a profound impact on the affected and surrounding patients, the care team, and the organizational plan of the day-hospitals. Although procedures to prevent SIRs are well established and homogeneous across countries and settings, occurring events were considered an occasion to reassess procedures and conduct full root-cause analysis. The introduction of specific tools, such as predictive biomarkers, to reliably identify high-risk patients and predict the occurrence of SIRs, would be highly appreciated by the practitioners to reduce the risk of fatal outcomes.

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Compliance with ethical standards

Conflict of interest George Kafatos, Peter Burdon, Kimberly Lowe, and Gaston Demonty are employees of Amgen and own shares in Amgen. Marjorie Leclerc and Alain Flinois are employees of Kantar Health, which received funding from Amgen Ltd, Uxbridge, UK, to conduct this research. Sabada Dube was a contract worker at Amgen Ltd during the time of study conduct, data interpretation, and manuscript preparation.

Data sharing Amgen holds the source data and the authors had access to the data. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://www.amgen.com/datasharing.

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