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The impact of infusion reactions associated with monoclonal antibodies in metastatic colorectal cancer: A European perspective

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Abstract

Background and objectives: Published data on the clinical and economic impact of infusion reactions to monoclonal antibodies are limited. This study investigated oncologists' and oncology nurses' opinions about resource use associated with infusion reactions and the impact on patient management in Europe.

Methods: Eighty oncologists and nurses from Denmark, France, Germany, Greece, Italy, Spain, Sweden and the UK currently treating patients with metastatic colorectal cancer were interviewed by telephone using a 27-item questionnaire developed for this study.

Results: The mean estimated number of staff (physicians and nurses) involved in managing an infusion reaction was 1.97 for a grade 1, 2.35 for a grade 2, 3.6 for a grade 3 and 5.3 for a grade 4 reaction. In respondents' experiences, most patients with grade 3 infusion reactions (73.4%) were admitted to hospital for treatment; 82.5% of those with grade 4 infusion reactions were treated in intensive care. The estimated duration of hospital treatment was 13.3 ± 29 h for a grade 3 infusion reaction, increasing to 48.1 ± 43.7 h for a grade 4 infusion reaction.

Conclusions: According to respondents, management of infusion reactions led to substantial resource use, which increased with the severity of the reaction. More severe reactions also led to anxiety in patients and distress to staff.

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Keywords

Infusion reactions, monoclonal antibodies, metastatic colorectal cancer

Introduction

Three monoclonal antibodies – bevacizumab (a humanized antibody against vascular endothelial growth factor (VEGF)) (Avastin[®], Genentech/Roche), cetuximab (a chimeric antibody against endothelial growth factor receptor (EGFR)) (Erbix[®], Merck Serono/Bristol-Myers Squibb) and panitumumab (a fully human anti-EGFR antibody) (Vectibix[®], Amgen Inc.) – have demonstrated improved clinical outcomes in patients with metastatic colorectal cancer (mCRC).^{1–9} All are associated with well-known adverse events but profiles differ between the monoclonal antibodies, particularly between the anti-VEGF and anti-EGFR antibodies. Infusion reactions occur with all the monoclonal antibodies but at different rates.^{10–13} The symptoms of infusion reactions range in severity from mild flushing to potentially life-threatening anaphylaxis.^{14,15}

Oncology clinics have well-established management strategies to deal with infusion reactions. Mild and moderate infusion reactions are typically treated in the outpatient setting, whereas severe infusion reactions require emergency measures and hospitalization. Medical therapy for infusion reactions may include adrenaline, corticosteroids, intravenous (IV) antihistamines, bronchodilators, oxygen and vasopressors.¹⁵

Although strategies for managing infusion reactions related to monoclonal antibody therapy are established, the resources required to manage infusion reactions are not well documented, particularly in Europe. The published literature on the impact of monoclonal antibody infusion reactions is limited mainly to data from the USA. Findings from these US studies suggest that: infusion reactions have a negative impact on patients and nurses, causing stress and anxiety¹⁶; and infusion reactions are treated using drugs and IV fluids and can require time in hospital.¹⁷ Additional staff time is required to manage a patient experiencing an infusion reaction, which adds to the costs of treatment.¹⁸ Treating a severe infusion reaction costs, on average, an additional US\$9308.¹⁹ The only published European study focused on the incidence of infusion reactions, without reporting on the resources needed to manage such reactions.²⁰

To address the lack of European data, this study was performed to investigate oncologists' and oncology nurses' opinions about the resource use associated

with infusion reactions and the impact of such reactions on patient management in real-world clinical practice in Europe.

Methods

Study objectives

The primary objective of the study was to describe healthcare providers' experiences of the resource use associated with infusion reactions in patients with mCRC receiving monoclonal antibody therapy. The secondary objective was to assess the perceived impact of infusion reactions on patient management (e.g. attitudes to treatment and treatment delays).

Study design

The study was based on telephone interviews with healthcare professionals from Denmark, France, Germany, Greece, Italy, Spain, Sweden and the UK. Oncologists and nurses currently treating mCRC patients participated in the interviews. Face-to-face interviews were conducted in Greece. There was no patient involvement or clinical intervention and no investigational products were used. The study was performed in two phases: a pilot phase and a main phase. The study protocol was reviewed by the Human Ethics Committee of the University of Technology Sydney, and considered to meet all ethical requirements and to be low risk.

Participants

Participants included oncologists and nurses who currently treated at least 10 new mCRC patients per month and who also had experience in the treatment and prophylaxis of monoclonal antibody infusion reactions within the previous 3 months. For the pilot phase of the study, participants were required to read, write and speak English sufficiently well to participate in the interview process. The exact split of healthcare professionals (oncologists versus nurses) varied between countries, reflecting differing patterns of care in each country.

Interview procedure

Potential respondents completed an electronic screening questionnaire before participating in the telephone interview. The interviewer first explained the background to the study and answered any questions. Infusion reactions were defined as any event within 24 h of an infusion during the clinical study described as an allergic or anaphylactoid reaction, or any event occurring on the first day of dosing described as an allergic reaction, anaphylactoid reaction, fever, chills or dyspnoea,^{10–12} and classification of severity was as shown in Table 2 in the Appendix. When asking questions about the treatment of infusion reactions, we made no attempt to ascertain which antibody was associated with the infusion reactions; we were interested in differentiating between the treatment of different severities of infusion reaction. The interview was then conducted on the basis of a specially developed questionnaire. Each interview lasted for 35–45 min. All interviews were conducted over a 6-week period in May–June 2010. All interviewers were trained on the interview procedure before the pilot phase of the study.

Pilot phase

The pilot phase was conducted to ensure the interview questions were unambiguous, appropriate and acceptable to respondents. In the first instance, a questionnaire was developed based on a review of the literature and input from oncologists. Two oncologists from each country (one from Greece) were then interviewed by telephone using the questionnaire as a basis. These interviews were conducted in English. Following the interviews, the questionnaire was refined to ensure clarity and appropriateness. This involved rewording any questions that were not well understood by respondents or were ambiguous. Pilot respondents were re-interviewed with any refined or additional questions. The main phase of the study was then conducted.

Main phase

Telephone interviews were conducted based on the final questionnaire. This was composed of 27 open-ended, semi-structured or multiple-choice questions relating to the treatment of infusion reactions. The classification system for the severity of infusion reactions used in the questions is shown in Table 2 in the Appendix. The final questionnaire was translated and administered in the local language.

Data analysis

Descriptive statistical analysis was performed on the pooled data from all eight countries. Data are presented as mean $\pm$ SD for continuous variables and as percentages for binary variables.

Results

Respondents

A total of 111 hospitals across eight European countries were contacted about study participation, and the first 10 oncologists or nurses from each country who agreed to participate were interviewed. A total of 15 oncologists were interviewed in the pilot phase and 65 oncologists and nurses were interviewed in the main phase, giving a total of 80 respondents (10 from each country). Of the 80 respondents, 50 (62.5%) were oncologists and 30 (37.5%) were nurses (Table 1). Respondents had been in their current role for an estimated 12.8 ± 7.4 years and the mean number of new mCRC patients treated per month was estimated at 19.9 ± 15.3 .

Treatment of infusion reactions: Hospital stay

Ward type. In respondents' experiences, the setting for the treatment of an infusion reaction depended on the severity of the reaction, with higher-grade reactions requiring treatment in more resource-intensive wards such as intensive care. For grade 1 and 2 infusion reactions, respondents reported that patients were generally treated in the oncologist's practice or the outpatient department where the infusion was administered. For grade 3 infusion reactions, respondents reported that the majority of patients (73.4%) were treated in hospital. For grade 4 infusion reactions, respondents reported that the majority of patients (82.5%) were treated in intensive care (Figure 1).

Duration of hospital treatment. In respondents' experiences, the duration of hospital treatment increased with the severity of the infusion reaction. It was estimated that patients with a grade 4 infusion reaction were treated for a mean of 2 days (48.1 ± 43.7 h) in intensive care, compared with 13.3 ± 29 h for patients with a grade 3 infusion reaction who required hospitalization (Figure 2).

Treatment of infusion reactions: Other resource use

Staff involvement. According to respondents, the estimated number of staff involved in managing an

infusion reaction increased with the severity of the reaction (Figure 3). For example, the mean number of nurses involved in managing a grade 1 infusion reaction was estimated at 1.25 ± 0.5 (range 1–3), compared with 2.5 ± 1.2 (range 1–8) for a grade 4 infusion reaction. Overall, the mean total number of staff (including nurses) involved in managing an infusion reaction was estimated at 1.97 for a grade 1, 2.35 for a grade 2, 3.60 for a grade 3 and 5.30 for a grade 4 reaction.

In all countries, most respondents reported that oncologists were responsible for the management of grade 2–4 infusion reactions. For grade 1 reactions, however, some respondents reported that reactions were managed by nurses without the involvement of an oncologist.

Table 1. Number of oncologists and oncology nurses interviewed from each country.

Country	Number of oncologists	Number of nurses	Number of hospitals
Denmark	10	0	10
France	5	5	10
Germany	10	0	10
Greece	5	5	6
Italy	5	5	10
Spain	5	5	8
Sweden	5	5	8
UK	5	5	9

Drug use. In respondents' experiences, the drugs most commonly used for the treatment of infusion reactions were antihistamines (76–91%), corticosteroids (65–91%) and antiemetics (34–36%). The pattern of drug use varied with the severity of the infusion reaction, with grade 3 and 4 reactions more likely than grade 1 and 2 reactions to be managed with adrenaline, histamine H₂-receptor blockers, narcotics, non-steroidal anti-inflammatory drugs (NSAIDs) and bronchodilators (Figure 4).

Equipment. According to respondents, estimated equipment use increased with the severity of infusion reaction (Figure 5). Grade 3 and 4 infusion reactions were considered more likely than grade 1 and 2 infusion reactions to require an electrocardiogram and the use of IV fluids and oxygen. Grade 4 reactions were considered more likely than lower-grade reactions to require use of a defibrillator and cardiopulmonary resuscitation.

Laboratory tests. The estimated use of laboratory tests increased with the severity of infusion reaction (Figure 6). For grade 1 reactions, 10% or fewer of respondents used haematology, chemistry or other tests, whereas for grade 3 and 4 reactions, 40–50% of respondents used haematology, more than 50% used chemistry and 15–20% used other tests.

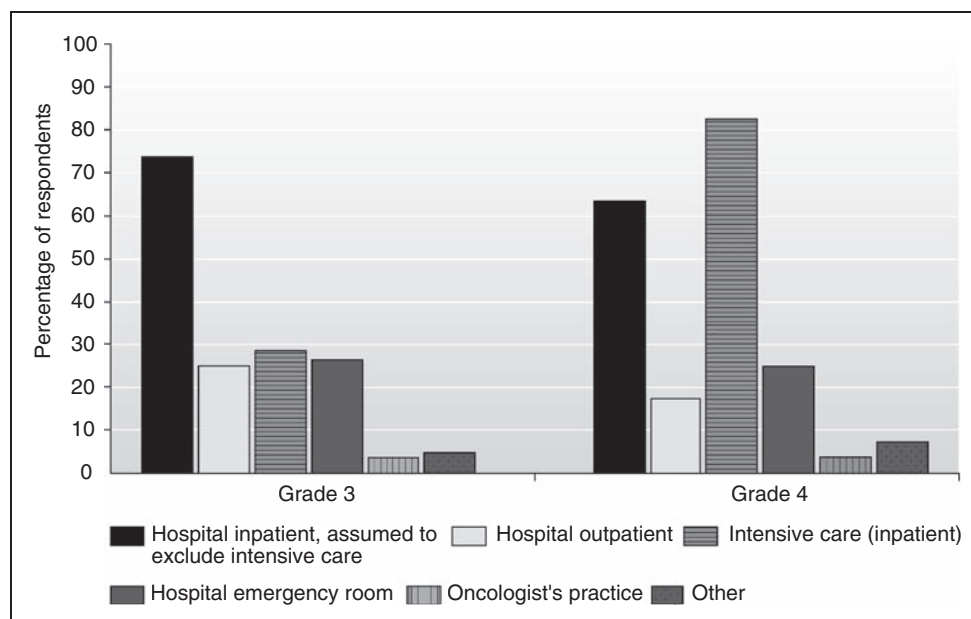


Figure 1. Perceived treatment settings for managing grade 3 and 4 infusion reactions (patients may be treated in more than one setting).

Follow-up visits. The number of follow-up visits was considered to increase with the severity of infusion reaction. Respondents estimated that grade 1 infusion reactions required a mean of 0.2 ± 0.6 follow-up visits, grade 2 infusion reactions required 0.3 ± 0.6 follow-up visits, grade 3 infusion reactions required 0.8 ± 1.4 follow-up visits and grade 4 infusion reactions required 1.0 ± 1.6 follow-up visits.

Impact of infusion reactions on antibody treatment regimens

Respondents estimated that 92% and 81.5% of patients who had grade 1 or 2 infusion reactions, respectively, were re-challenged, compared with only 19.8% and 5.1% of those who experienced grade 3 or 4 infusion reactions, respectively.

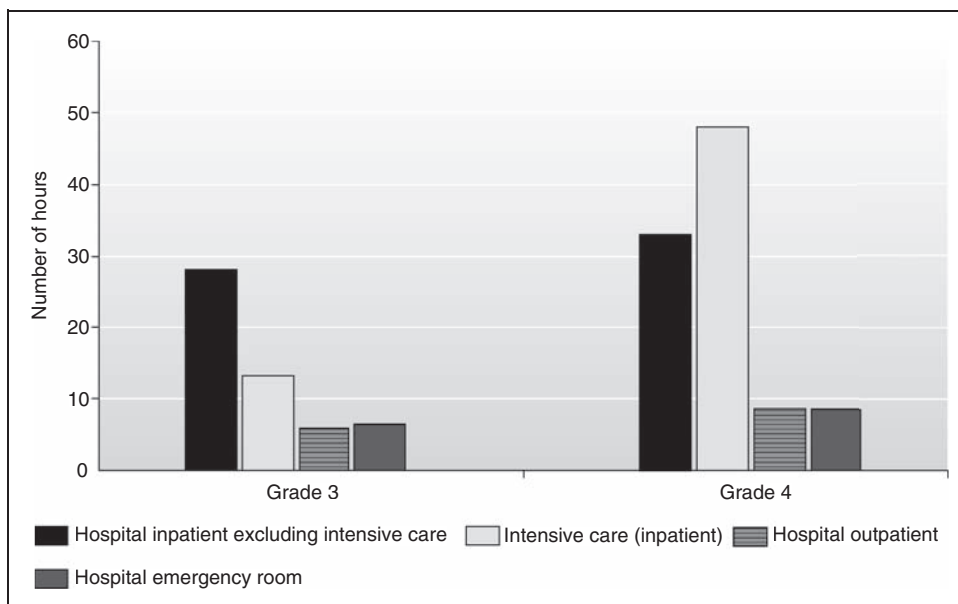


Figure 2. Mean estimated time in each setting for the treatment of grade 3 and 4 infusion reactions.

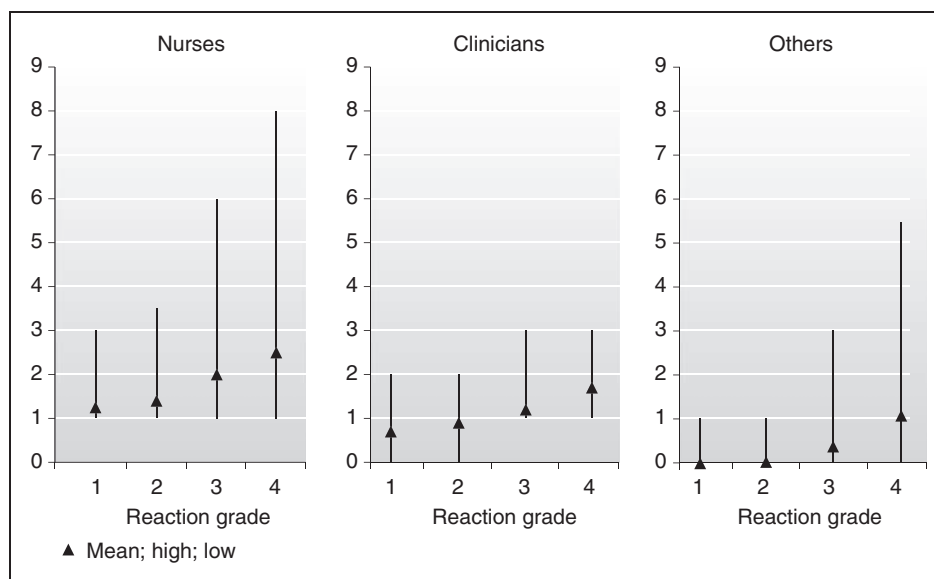


Figure 3. Estimated staff numbers involved in managing infusion reactions according to the grade of the reaction. NSAID: non-steroidal anti-inflammatory drug.

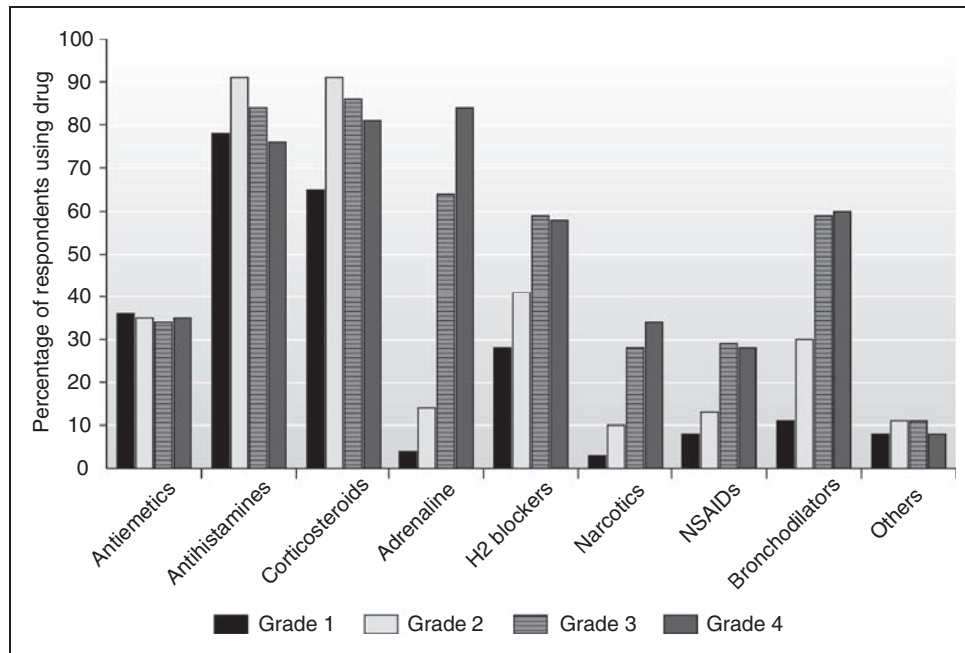


Figure 4. Perceived pattern of drug use for managing infusion reactions according to the grade of the reaction.

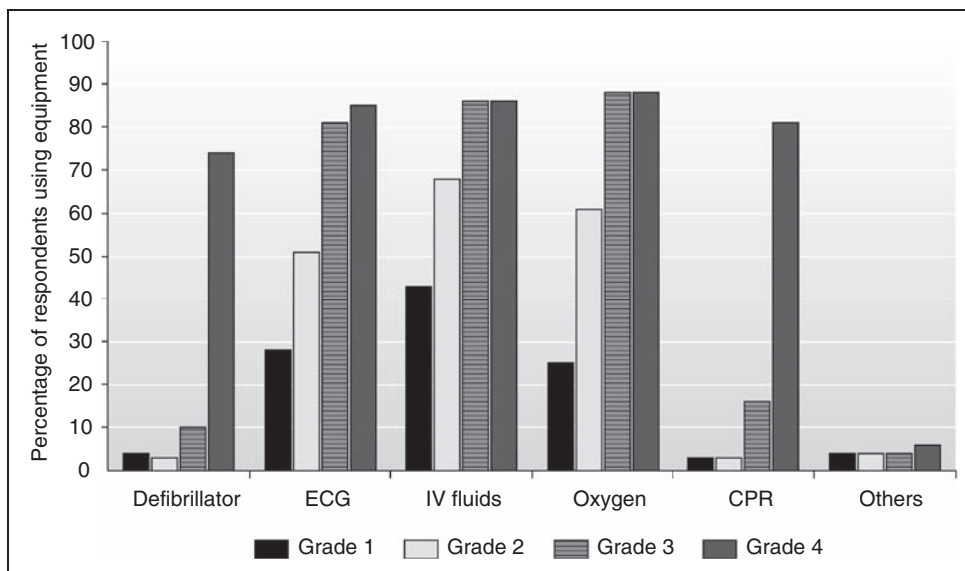


Figure 5. Estimated equipment use associated with the management of infusion reactions according to the grade of the reaction. CPR: cardiopulmonary resuscitation; ECG: electrocardiogram; IV: intravenous.

All grades of infusion reaction were considered to result in treatment delays before re-challenge; these delays were estimated to be longest in the few cases where re-challenge occurred after a more severe infusion reaction. The mean time to re-challenge was estimated at 30–40 h for grade 1 or 2 infusion reactions and 90–120 h for grade 3 or 4 infusion reactions.

The mean duration of infusion on re-challenge after an infusion reaction in response to the initial infusion was estimated at 108 min following a grade 1 infusion reaction, 129 min following a grade 2 infusion reaction, 174 min following a grade 3 infusion reaction and 232 min following a grade 4 infusion reaction.

In respondents' experiences, dose reduction during re-challenge was uncommon but was more likely after

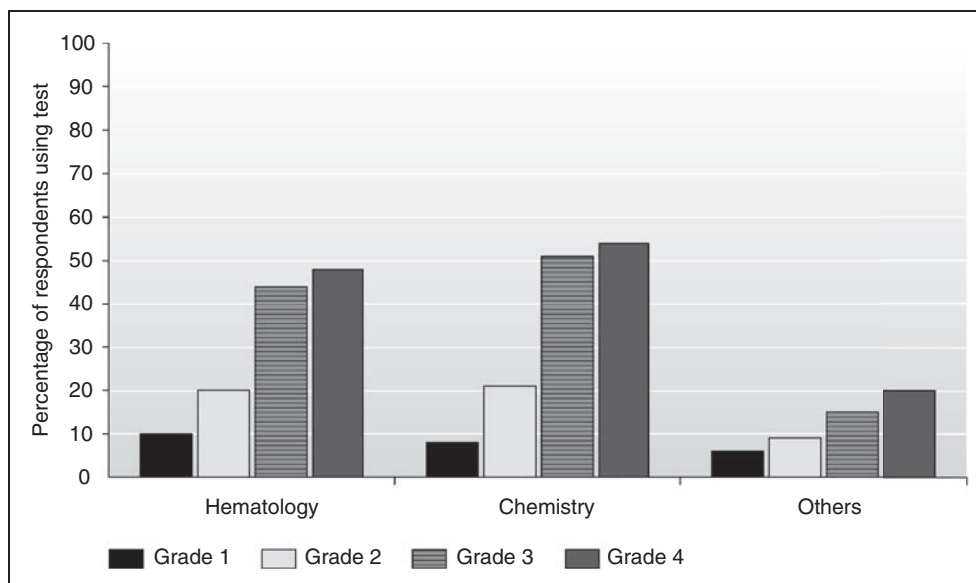


Figure 6. Estimated use of laboratory tests according to the grade of infusion reaction.

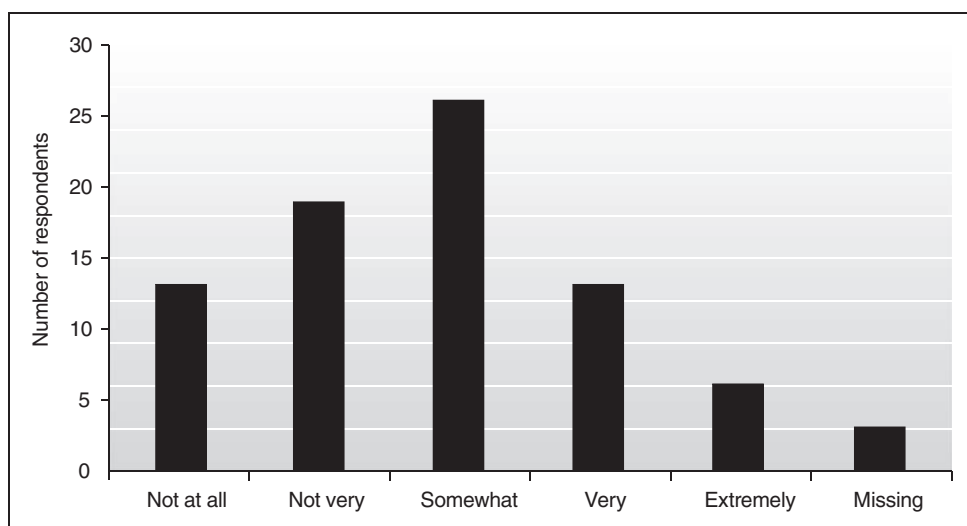


Figure 7. Perceived impact of infusion reactions on patients: oncologists' and oncology nurses' responses to the question 'In your experience, how concerned is the average patient about infusion reactions?'.

a grade 3 or 4 infusion reaction than after a grade 1 or 2 infusion reaction.

Impact of infusion reactions on patients, relatives and medical staff

Healthcare professionals' views on the impact of infusion reactions on patients varied (Figure 7). However, it was generally recognized that patients are usually anxious after an infusion reaction and some may not wish to continue treatment. Respondents' perceptions of the impact of infusion reactions on relatives and staff also

varied. Again, it was recognized that infusion reactions may cause stress and worry for the relatives of patients. However, a number of respondents commented that relatives do not always know about infusion reactions until after the event because they are not allowed to be present during treatment. According to respondents, infusion reactions may also cause stress for staff. However, the psychological impact of infusion reactions on staff does not appear to be as great as that on patients and relatives; many respondents commented that infusion reactions are not a concern because staff are trained to manage these reactions using standard procedures.

Country differences

The differences between countries in estimated resource use and the perceived impact of infusion reactions on patient management were examined descriptively. No statistical analysis was performed owing to the small sample sizes. Similar findings were observed across the eight European countries.

Discussion

The results of this study indicate that infusion reactions lead to substantial resource use, which increases with the severity of reaction. In respondents' experiences, more severe infusion reactions (grades 3 and 4) are associated with an increased need for hospitalization and more staff, drug use, equipment use and diagnostic testing. With regard to hospitalization, more severe infusion reactions were considered to be associated with longer hospital stays in more costly wards such as intensive care. In addition, all infusion reactions were considered to result in treatment delays, with more severe infusion reactions being associated with longer treatment delays prior to re-challenge. No data from clinical trials to quantify the impact of treatment delays on treatment efficacy could be found in the literature.

Infusion reactions were also recognized as having an impact on patients, relatives and medical staff, with respondents commenting that infusion reactions can cause anxiety and fear of further treatment.

In Germany and Denmark, we were able to obtain only the opinions of oncologists; nurses in these countries were unwilling to participate in the study because of restrictions placed on them by the hospitals in which they work. Overall, however, findings were similar across the eight European countries.

Published literature on the impact of infusion reactions is limited mainly to data from the USA. A retrospective chart review of 76 patients who experienced severe infusion reactions with monoclonal antibody therapy investigated the clinical consequences of these reactions. The results showed that 22% of such patients required hospitalization, for a mean of 4 days (range 2–6 days).¹⁷ The most common premedications were antihistamines and paracetamol, while typical post-infusion reaction management included oxygen, IV fluids and, as found in this study, corticosteroids.

Another US study investigated the impact of infusion reactions on oncology patients and nurses in both inpatient and outpatient settings through interviews with 202 nurses.¹⁶ In agreement with the findings from our survey, the results suggested that infusion reactions have a significant negative impact on both patients and nurses. Most nurses (96%) considered

grade 3 and 4 infusion reactions to be 'very' or 'extremely' disruptive for patients and 80% indicated that such reactions were disruptive to nurses, whereas only half of the nurses considered grade 1 or 2 infusion reactions to be 'very' or 'extremely' disruptive to patients and 30% considered such reactions to be disruptive to nurses. Most nurses indicated that patients experienced fear or apprehension related to an infusion reaction, and nearly all agreed with the statement that infusion reactions can result in lost time and increased patient anxiety. About three-quarters of nurses agreed that infusion reactions add a tremendous amount of stress and anxiety to staff and approximately half agreed that infusion reactions are very draining and frightening for nurses.¹⁶

Finally, in a recent analysis of a US administrative claims database, infusion reactions requiring medical intervention were found to occur in 8.4% of cetuximab-treated patients. In addition, 68% of cetuximab-treated patients experienced treatment disruptions and 34% discontinued treatment. The mean treatment cost for an infusion reaction requiring emergency room treatment or hospitalization was US\$9308.¹⁹

These findings from the published literature are consistent with those of this study, in which infusion reactions led to substantial resource use and caused anxiety and fear for patients, relatives and healthcare providers. However, our study provides more details than previous publications on the estimated impact of infusion reactions by grade.

This study has some limitations. First, it is difficult to clearly define infusion reactions.¹⁵ We used a definition based on the European Medicines Agency labels for the antibodies that included anaphylactoid or allergic reaction, fever, chills or dyspnoea. These symptoms were not further defined as we believe the local clinical definitions are relevant and appropriate. This limitation could be resolved in future studies by providing additional definitions. In addition, resource use was estimated based on the opinions of respondents, not actual use of resources to treat infusion reactions. However, respondents were healthcare professionals with first-hand experience of treating infusion reactions. This could be addressed in future research by performing a retrospective chart review or by prospectively monitoring infusion reaction management. Furthermore, the impact of infusion reactions on patients, relatives and healthcare providers was also based on the opinions of respondents rather than on actual experiences. This could be addressed in future research by interviewing oncologists and nurses using a questionnaire that specifically addresses the impact of infusion reactions on healthcare providers and by interviewing patients and relatives directly using patient- and relative-specific questionnaires. We acknowledge the subjective nature of the estimates and opinions

obtained by questionnaire in this study, which should be borne in mind when interpreting the data presented. Despite this, respondents were healthcare professionals with first-hand experience of treating infusion reactions. Thus, despite limitations, this study has produced useful information on the perceived clinical and economic impact of infusion reactions in patients with mCRC in eight major European countries. Further research to assess the incidence, severity and impact of infusion reactions caused by each monoclonal antibody in clinical practice would build on these findings.

Conclusions

In the experience of oncologists and oncology nurses, the management of infusion reactions associated with monoclonal antibody therapy in mCRC in real-world clinical practice across eight European countries requires substantial resource use, which increases with the severity of the infusion reaction.

Funding and conflicts of interest

Shkun Chadda, Mark Larkin, Clare Jones and David Sykes are employees of PRMA Consulting Ltd and received research funding from Amgen Inc. Beth Barber, Zhongyun Zhao and Sue Gao are employees and stockholders of Amgen Inc. Nils-Olof Bengtsson received funding from Amgen Inc. for his participation in this study. This study was concerned with the treatment of infusion reactions caused by the three antibodies indicated for the treatment of mCRC. Amgen Inc. is the manufacturer of one of these antibodies (panitumumab).

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Appendix

Table 2. Classification system for the severity of infusion reactions.²¹

Grade	Acute infusion reaction (cytokine release syndrome)
1	Mild reaction; infusion interruption not indicated; intervention not indicated
2	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics and IV fluids); prophylactic medication indicated for longer than 24 h
3	Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates)
4	Life-threatening; pressor or ventilator support indicated
5	Death

IV: intravenous; NSAIDs: non-steroidal anti-inflammatory drugs.