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Classification of antineoplastic drug-induced tissue damage: a Consensus of the Spanish Oncology Pharmacy Group

Clasificación del daño tisular de antineoplásicos: Consenso del Grupo Español de Farmacia Oncológica

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Abstract

Objective: To reach at an expert consensus, using the Delphi method, for classifying the tissue-damaging potential of antineoplastic drugs, in order to facilitate the decision-making process in the event of extravasations.

Method: The panel of expert evaluators was made up of seven pharmacists belonging to the working group on extravasations. Other member served as coordinator. The likelihood of tissue damage was reviewed on the basis of eight reference documents. Four categories of drugs were established: vesicant (V); high risk irritant (HRI); low risk irritant (LRI) and non-irritant (NI). Two rounds of surveys were performed. The drugs with an agreement of less than 70% after the two rounds were discussed non-anonymously by the group. For each of the rounds the following was analysed: median of the degree of consensus and the interquartile range (IQR_{25-75}), degree of agreement by tissue damage category, and percentage of antineoplastics reaching a degree of consensus of over 85% and of 100%. Drugs whose classification differed in the various reference documents were assessed separately. SPSS v23.0 statistical software was used.

KEYWORDS
Delphi technique; Vesicant; Irritant; Extravasation of diagnostic and therapeutic materials; Antineoplastics; Cytostatics; Chemotherapy; Soft-tissue damage.

Resumen

Objetivo: Realizar un consenso de expertos utilizando el método Delphi para la clasificación del potencial de daño tisular de los antineoplásicos que facilite la toma de decisiones ante una extravasación.

Método: El panel de evaluadores estaba formado por siete farmacéuticos del grupo de trabajo de extravasaciones. Otro actuó como coordinador. Se revisó la probabilidad de daño tisular a partir de ocho documentos de referencia. Se clasificaron en cuatro categorías: vesicante, irritante de alto riesgo, irritante de bajo riesgo y no irritante. Se realizaron dos rondas; tras éstas los fármacos con consenso < 70% se discutieron en grupo de forma no anónima. Se analizó para cada ronda: la mediana del grado de consenso y ámbito intercuartílico (AIQ_{25-75}), el grado de concordancia por categoría de daño tisular y el porcentaje de antineoplásicos con grado de consenso > 85% y del 100%. Se analizaron de forma separada los fármacos con discordancias de clasificación entre los documentos consultados. Se utilizó el programa estadístico SPSS v23.0.

PALABRAS CLAVE
Técnica Delphi; Vesicantes; Irritantes; Extravasación de materiales diagnósticos y terapéuticos; Antineoplásicos; Citostáticos; Quimioterapia; Lesión en tejidos blandos.

Results: Seventy-one antineoplastics were evaluated. In the first round, the median for degree of consensus was 100.0% (IQR_{25-75}: 71.4-100.0%). In the second round, the median was 100.0% (IQR_{25-75}: 85.7-100.0%). The percentage of antineoplastics with a consensus of 85.7% or above increased from 66.7% to 85.9% in the second round. For the 30 antineoplastics whose values differed in the reference documents, the degree of agreement increased from 71.4% (IQR_{25-75}: 57.1-87.7%) to 100.0% (IQR_{25-75}: 85.7-100.0%) in the second round. The percentage of antineoplastics with a consensus of 85.7% or above increased from 40.0% to 76.7%. Four antineoplastics had a degree of agreement of less than 70.0%. The final classification of drugs per category, was: 17 vesicants; 15 HRI; 13 LRI; and 26 NI. The final degree of consensus was 85.7% or above for 90.1% of antineoplastics, and 100.0% for 74.6% of the same.

Conclusions: In this area of scarce evidence and high variability, the Delphi method allows for consensus in classifying tissue damage risk, thus making it easier to reach clinical decisions. In approximately 90% of the antineoplastics, the degree of consensus reached by the expert panel was 85% or above. In 74% of the antineoplastics, it was 100%. This provides solid ground for management decisions.

Resultados: Se evaluaron 71 antineoplásicos. En la primera ronda la mediana del grado de consenso fue 100% (AIQ_{25-75}: 71,4-100,0%) y en la segunda ronda 100% (AIQ_{25-75}: 85,7-100,0%). El porcentaje de antineoplásicos con consenso ≥ 85,7% aumentó del 66,7% al 85,9% en la segunda ronda. Para los 30 antineoplásicos con discrepancias entre los documentos revisados, el grado de consenso aumentó del 71,4% (AIQ_{25-75}: 57,1-87,7%) al 100% (AIQ_{25-75}: 85,7-100,0%) en la segunda ronda. El porcentaje de antineoplásicos con concordancia ≥ 85,7% pasó del 40,0% al 76,7%. Cuatro antineoplásicos presentaron consenso < 70%. La clasificación final incluyó 17 fármacos como vesicantes, 15 como irritantes de alto riesgo, 13 como irritantes de bajo riesgo y 26 como no irritantes. El grado de acuerdo final fue ≥ 85,7% en el 90,1% de los antineoplásicos y del 100% en el 74,6%.

Conclusiones: En este área de escasa evidencia y variabilidad la metodología Delphi permite alcanzar un consenso de clasificación del riesgo de daño tisular que facilita la toma de decisiones. Aproximadamente para el 90% de los antineoplásicos el grado de concordancia alcanzado por el panel de expertos fue > 85%, y para el 74% de los antineoplásicos la concordancia fue del 100%, aportando una base sólida para las decisiones de manejo.

Introduction

Tissue damage associated with antineoplastic extravasation is an adverse event related with intravenous drug administration, whose risk varies greatly. Severity may range from mere erythema to tissue necrosis that even requires surgical debridement[1]. The incidence of extravasations reported is between 0.10% and 6.00% in peripheral venous administrations. In central venous administrations it is lower (0.26% to 4.7%) but more severe[2]. These values have come down in recent years, and currently range between 0.05% and 5.00%, thanks to improvements in training and to the implementation of strategies to minimise the incidence of extravasations[3]. Prevention is the best way to manage extravasations, but immediate action is necessary when they occur, in order to avoid or minimise associated tissue damage, which can compromise the clinical outcome of patients due to potential delays in their antineoplastic regimen, and also affect their safety and their quality of life.

Hospitals have protocols for the management of extravasations. These may be institutional or regional, and are approved by multidisciplinary consensus, serving as a guide for implementation on the basis of the tissue-damage classification of the involved drugs. It is therefore important to be familiar with the risk of tissue damage, with a view to making decisions relating to protocols and clinical practice. However, classifications vary depending on the source of reference, and there is even variability in the categories used to classify antineoplastics in terms of their potential for causing tissue damage[4-6], which is usually defined on the basis of maximum described toxicity levels. Depending on the probability of extravasation-related damage, antineoplastics are classified in three categories (vesicant, irritant and non-irritant) or five (vesicant, exfoliant, irritant, inflammatory, and neutral). The first of these two classifications is the most frequently used in the literature. Regarding potential for tissue aggression, and although this depends mainly on the type of cell-damage mechanism involved, a series of variables come into play: concentration, extravasated volume, and pH and osmolarity, among others[7,8]. This adds further difficulty to antineoplastic classification.

Information on the effect and evolution of extravasations is largely based on cases series or case reports, with the exception of two small clinical trials involving dexrazoxane[9]. Little information is available regarding tissue damage in the technical description sheets of drugs. In some instances, data are derived from animal studies, which cannot be extrapolated to humans, while in other cases they are taken from outdated studies based on techniques and administration methods that are no longer in current use. In view of the scarcity of evidence and the degree of variability among the classifications proposed in the different guidelines, the working group on extravasations of the Spanish Oncology Pharmacy Group (GEDEFO), belonging to the Spanish Society of Hospital Pharmacists (SEFH), decided to apply the Delphi methodology to arrive at a consensus with regard to the tissue damage classification of antineoplastic drugs.

The Delphi method is an expert consensus technique that has been used in the field of healthcare when scientific evidence is either not available, scarce, or poor in quality; in such scenarios, the experience and accuracy of group judgements is considered to be superior to those of individual approaches, since they bring together the knowledge and experience of all group members[10,11]. In addition, the method preserves voting anonymity among the evaluators, thereby guaranteeing independent decisions on the part of group members. Other advantages include the fact that all panellists have equal opportunities when contributing to the final decision, and that the procedure is decentralised, with information and decisions being aggregated by summarising the results[12]. This methodology has been used in the hospital pharmacy practice to design satisfaction surveys, set up the taxonomy for pharmaceutical interventions, select training goals, or define quality indicators, among other objectives[13-16].

The goal of the present paper is to establish a consensus of experts, by using the Delphi method, that can be used to classify the tissue-damaging potential of antineoplastic drugs, in order to facilitate the decision-making process in the event of extravasations.

Methods

The modified Delphi method was applied to classify antineoplastic drugs according to their potential for extravasation-related tissue damage, based on a consensus of experts. The panel of expert evaluators included seven pharmacists with oncological training, who were members of the GEDEFO's Extravasation Working Group and had previous expertise and publications dealing with this issue. Other of the group members served as coordinator. The study was carried out from October to December of 2019.

For the classification of antineoplastic drug-induced tissue damage, eight reference documents were selected, following preliminary research by the working group, which involved the examination of clinical extravasation guidelines published by scientific societies or institutions, routinely used databases, and reference papers dealing with extravasations[4-6,17-21]. In addition, and in order to identify emerging risks or new tissue-damage evidence, the scientific bibliographical search used in the *Monograph for Prevention and Treatment in cases of antineoplastic extravasations* was reviewed on PubMed database (search terms: "Antineoplastic Agents" [Mesh]) AND "Extravasation of Diagnostic and Therapeutic Materials" [Majr]. Filters: population, humans; language: English, French, Spanish. Advanced filters: title "extravasation". Period: 01/01/2010-30/09/2019)[22].

The present consensus has adopted the standard classification of tissue toxicity (vesicant, irritant, non-irritant) since it is the most frequently used in published studies and guidelines, but includes the modification proposed by Conde-Estévez *et al.*[18], which distinguishes between high-risk and low-risk irritant antineoplastics, because of the differences in the management to prevent potential patient morbidity. Antineoplastics have therefore

Table 1. Definition of tissue-damage categories in cases of extravasation

Non-irritant (NI)	Antineoplastics with no tissue aggression potential; they do not normally cause irritation when extravasated.
Low risk irritant (LRI)	Antineoplastics that can cause local irritation that may be associated with pain, a burning sensation or pressure, with or without signs of local inflammation and phlebitis, both at the injection site and along the vein; no necrosis or ulceration develop in most cases.
High risk irritant (HRI)	Antineoplastics that can cause damage such as is associated with LRI drugs, with confirmed cases having been described of lesions that are compatible with vesicant damage.
Vesicant (V)	Antineoplastics that may cause local or extensive tissue necrosis, with or without ulceration, and complete loss of skin thickness and underlying structures.

been classified in four categories, depending on the probability of tissue damage in the event of extravasation: vesicant (V); high risk irritant (HRI); low risk irritant (LRI); and non-irritant (NI). Table 1 summarises the definition for each category. Radionuclide conjugated monoclonal antibodies have been excluded from the classification, since tissue damage is in their case mainly associated with radiation, and their management differs from that of the rest of antineoplastics, hormone therapy, drugs that are currently not available in the therapeutic armamentarium, such as mechlorethamine, and investigational antineoplastic agents. Non-conjugated monoclonal antibodies were considered as a single group in terms of the classification.

The coordinator prepared an initial table indicating the category of tissue damage assigned to each antineoplastic on the basis of the eight reference documents, and this was sent by e-mail to each of the expert panel members. Based on the information included in that document, and on their own professional experience, evaluators issued their classifications (first round) which were returned to the coordinator. The latter examined the degree of agreement (percentage of evaluators in the most voted category) and the comments of group members, and issued a new document indicating the category with the highest score for each antineoplastic and including comments that were proposed anonymously. This new information was sent individually to each expert, for re-evaluation or confirmation of his/her previous classification (second round).

If agreement in the classification of any given antineoplastic was lower that 70% (5/7 members of the panel) at the end of the second round, the case was appraised individually, on the basis of additional information research and non-anonymous group discussion, and a joint decision was reached.

Finally, the definitive classification was sent to all group members, for individual approval. This classification has been included in the *Monograph for Prevention and Treatment in cases of antineoplastic extravasations* that was prepared by the group[22].

In each round, the median of the degree of consensus with the interquartile range (IQR_{25-75}) was examined, and for each category of tissue-damage risk the rate for agreement was analysed. The percentage of antineoplastics with a consensus of above 85%, and of 100%, was calculated. If agreement was above 80%, consensus was considered to be strong[11,23]. A separate analysis of the consensus achieved was performed considering only the drugs with discrepancies between their classification in the different reference documents and the rate for agreement reached.

Statistical work was performed using IBM SPSS v23.0 software (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY).

Results

After applying the defined exclusion criteria, 71 antineoplastics were selected to evaluate their tissue-damage risk, non-conjugated monoclonal antibodies were considered a single agent. On the basis of the search strategy that was employed, no additional literature was found to provide new information regarding the tissue-damaging potential of the antineoplastics that were being classified. Non-conjugated monoclonal antibodies were classified, by unanimous agreement, as NI.

In the first round, the median rate of consensus was 100.0% (IQR_{25-75}: 71.4-100.0%). Of the total amount of evaluated antineoplastics, 18 drugs were classified as vesicant, 13 as HRI, 14 as LRI, and 26 as NI. In 66.7% (48/71) of the antineoplastics, the rate for agreement was 85.7% or above. Consensus was 100.0% in 52.1% (37/71) of the antineoplastics.

Thirty antineoplastics (42.3%) exhibited tissue-damage classification variability in the different reference documents; in these, the median rate for agreement was 71.4% (IQR_{25-75}: 57.1-87.7%). Of the 30 drugs, 3 were classified as vesicant, 10 as HRI, 8 as LRI, and 9 as NI. In 40.0% of them (12/30), the rate of consensus was 85.7% or above.

In the second round, the median rate of consensus was 100.0% (IQR_{25-75}: 85.7-100.0%). None of the antineoplastics modified their classification in the second round, but the percentage of agreement increased. In 85.9% (61/71) of the analysed antineoplastics, the degree of consensus among the experts was 85.7% or above; in 71.8% (51/71) a consensus of 100.0% was reached.

The median for rate of consensus of the 30 antineoplastics whose classification varied in the reference documents was 100.0% (IQR_{25-75}: 85.7-100.0%) in the second round. None of the antineoplastics changed their classification. In 76.7% (23/30) of the antineoplastics, the rate for agreement was 85.7% or above.

Tables 2 and 3 show the rate for agreement in the classification of tissue-damage risk between the first and second round for each category of tissue damage. The agreement percentage is lower for both categories of irritant drugs.

At the end of the second round, only four antineoplastics exhibited a degree of consensus that was below 70%: busulfan, carmustine, etoposide phosphate, and treosulfan. They were subject to non-anonymous group discussion. For carmustine and busulfan a consensus of 100.0% was reached;

Table 2. Rate for agreement in the classification of antineoplastics according to their tissue-aggression potential in cases of extravasation. First round

	Agreement in the first round					
	42.9%	57.1%	71.4%	85.7%	100.0%	TOTAL
Non-irritant	1	1	5	3	16	26
Low risk irritant	0	2	3	5	4	14
High risk irritant	3	3	1	3	3	13
Vesicant	1	2	1	0	14	18
TOTAL	5	8	10	11	37	71

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Table 3. Rate for agreement in the classification of antineoplastics according to their tissue-aggression potential in cases of extravasation. Second round

	Agreement in the second round					
	42.9%	57.1%	71.4%	85.7%	100.0%	TOTAL
Non-irritant	0	1	1	1	23	26
Low risk irritant	0	0	2	2	10	14
High risk irritant	0	1	3	4	5	13
Vesicant	0	2	0	3	13	18
TOTAL	0	4	6	10	51	71

consensus for treosulfan was 85.7%. In the case of etoposide phosphate, the level of agreement remained below 70.0%.

The final consensus on the classification of the antineoplastics, according to their potential for causing tissue damage in the event of extravasation, is summarised in table 4: 17 were classified as vesicants; 15 as HRI; 13 as LRI; and 26 as NI. In 90.1% of the antineoplastics (64/71) the rate for agreement of the reviewers, regarding tissue damage classification, was 85.7% or above. In 74.6% of the drugs (53/71) consensus was 100.0%.

If we refer these values to the analysis of the 30 antineoplastics which exhibited variability in their classification in the literature, we find that in 86.7% of them (26/30) the rate of consensus was 85.7% or above. In 60.0% (18/30) it was 100.0%.

Discussion

The Delphi method is a consensus methodology that allows for decision-making in scenarios of uncertainty, and is widely used in healthcare in general and pharmacy in particular. In that context, the opinions of the expert panel members may help professionals to make decisions and generate new ideas, and the method has been used to develop guidelines, design guides, and define indicators or clinically significant interactions[11,23-26].

There is no standard method for calculating the number of experts needed in order to apply the Delphi method; this depends on the objective of the study and the sources available[10]. In published studies, the number of experts varies, and usually includes about 12 to 15[12,14,25], although in gene-

Table 4. Consensus on classification of antineoplastics according to their tissue-aggression potential in cases of extravasation

Vesicant	High risk irritants	Low risk irritants	Non irritant
amsacrine	bendamustine	arsenic trioxide	aflibercept
carmustine	busulfan	cabazitaxel	aldesleukine
DACTINomycin	CISplatin*	CARBOplatin**	asparaginase
DAUNOrubicin	dacarbazine	etoposide**	azaCITIDine
DOXOrubicin	DAUNOrubicin LIPOSOMAL&	etoposide phosphate	bleomycin
epirubicin	dexrazoxane	fluorouracil**	bortezomib
IDArubicin	DOCEtaxel	fotemustine	brentuximab vedotin
mitomycin	DOXOrubicin LIPOSOMAL&	gemcitabine	carfilzomib
mitoXANTRONE	(pegylated/non pegylated)	ifosfamide	cladribine
PACLitaxel	melphalan	irinotecan	clofarabine
trabectedin	oxaliplatin	irinotecan LIPOSOMAL	crisantaspase
vinBLAStine	PACLitaxel albumin-bound	ixabepilone	cyclophosphamide
vinCRIStine	streptozocin	topotecan	cytarabine
vinCRIStine LIPOSOMAL&	trastuzumab emtansine		eriBULin
vindesine	treosulfan		fludarabine
vinflunine			gemtuzumab ozogamicin
vinorelbine			inotuzumab ozogamicin
			methotrexate
			monoclonal antibodies (non-conjugated)
			nelarabine
			pegasparaginase
			pemetrexed
			pentostatin
			raltitrexed
			temsirolimus
			thiotepa

* Cisplatin: concentrations of above 0.4 mg/mL are classified as vesicant.

** High concentrations of carboplatin (≥ 5 mg/mL), etoposide (≥ 10 mg/mL) or fluorouracil are associated with a greater tissue-damage risk.

& Liposomal presentations have a lower risk of causing tissue damage, but little information is available.

ral it is considered that the minimum required number would be 7, and the maximum number would be 30[10,13,16]. The number of experts in the present study's panel met that criterion.

Regarding the number of evaluations required for reaching consensus, most studies have used two waves or two rounds, although there are differences between the published papers; in general, as a function of the degree of consensus achieved, the Delphi process is discontinued when the predefined consensus level have been reached[12,14,25,27]. In the present work, after the second round, a degree of consensus of above 85% was reached for more than 80% of the antineoplastics. By category of tissue aggression, the rate of consensus achieved was lower for irritant antineoplastics (both HRI and LRI); this is related to the subclassification introduced to take account of the differences in management of extravasations. Mader recommends the use of the standard classification, since it is still the most widely employed, but points out that other authors propose additional categories (five grades) in an attempt to improve both the classification and the management of extravasations[6,8], which was also the objective of the present study.

The rate for agreement that is considered to be high level is different for the various published studies, ranging from 81.8% to 90.0%[12]. Some authors propose a minimum agreement rate of 80% as a consensus threshold[24]. When numerical values are used (scoring methods such as the Likert scale, for instance) a median of 77.77% or above is considered adequate[11]. When at least one third of the evaluators differ from the rest, no agreement or consensus is considered to have been reached[11]. If we apply the four categories of evidence and consensus of the National Comprehensive Cancer Network (NCCN) criteria (from a higher to a lower level of evidence and consensus: 1, 2A, 2B and 3), the recommendations of the present expert panel would fit into category 2A for most of the antineoplastics, since they are based upon lower-level evidence, but with a uniform classification consensus[28].

Although expert consensus is considered to be the lowest level on the pyramid of scientific evidence, the strength of an expert consensus depends not only on the input available to the experts (systematic reviews, individual experiments, personal experience and qualitative studies) but also on the methodology used to achieve consensus[26]. In spite of its limitations, the present consensus is a starting point that establishes a practical basis for recommendations in the management of extravasations of the different antineoplastics, with the aim of reducing variability in patient care.

It is important to point out that classifications have traditionally been based on the highest grade of toxicity reported, irrespective of its actual frequency, even when anecdotal, or influenced by other factors related to the patient or the procedure, which could condition the final level of damage and the patient outcomes. A publication bias cannot be ruled out in cases whose consequences are more severe in the event of extravasation. Such bias may affect the classification by overestimating risk.

The leading factor in tissue damage is the mechanism of action, at cell or molecular level, of each cytotoxic; however, other aspects also contribute to tissue damage, and these include concentration, extravasated volume, ph (≤ 5 or ≥ 9), osmolarity (> 500 mOsm/L), excipients (Polysorbate 80 or Cremophor EL® increase irritating properties), formulation (liposomes), location, and the time that elapses from the moment of extravasation until the latter is detected[7]. Although these variables are not always described in the published case reports, they may affect the final outcome, and therefore influence the classification and the variability found in the literature.

Thus, the distinction between a vesicant or an irritant antineoplastic is not absolute, and depends on other factors: concentration, for example, is a variable that in most guidelines causes cisplatin to be considered HRI if it equals 0.4 mg/mL or above, or vesicant if it is below that value. It has recently been suggested that the administration of diluted vincristine reduces its tissue-damaging potential as compared to the concentrated preparation (1 mg/mL)[29]. Liposomal presentations are considered to be less likely to cause lesions that are compatible with vesicant damage, although no distinction is normally made between the pegylated and non-pegylated formulations. The expert panel considers that liposomal presentations are associated with a lower risk of tissue damage, although little information and published experience are available. Information is even scarcer with regard to antineoplastics that have been added to clinical practice in recent times. If no data are available regarding the tissue-aggression risk of a given drug, it is recommended to classify it as an irritant if it causes phlebitis and/or sclerosis at the injection site or along the vein[22]. The expert panel recommends adopting the tissue damage classification when a new antineoplastic drug is approved for use at each institution, and updating it as new information becomes available.

The only drug whose final agreement was below 70% was etoposide phosphate, which is not included in many of the reviewed reference documents (or not differentiated from standard etoposide), probably because of the greater weight of the evaluators' personal experience regarding the classification of the reference documents, since the excipient of the standard etoposide is considered to contribute to potential tissue damage.

The present tissue-risk classification consensus provides significant differences as compared to previous classifications in the reference documents: it updates the included drugs, divides drugs into HRI and LRI categories, on the basis of their different management approaches, and uses an explicit consensus methodology that is widely employed in the field of healthcare. Thus, by applying the same exclusion criteria of the present study to the drugs that were classified in the reviewed reference documents, the tissue-damage risk of 26 drugs that were not included in the Micromedex database[21], and 30 drugs not included in Uptodate[20], has been classified, as well as 15 additional drugs that were not included in the most recent or permanently updated guidelines[5,19]. The classification that has been introduced distinguishes potential severity in the event of extravasation of an irritant antineoplastic agent, with a view to guiding management and subsequent follow-up[18]. The greatest classification differences in the various guidelines apply to irritant drugs, with regard to which different terminologies are even used; this is the case, for example, in irritants with vesicant properties, inflammatory agents and exfoliantdrugs[6]. Lastly, no specifications regarding the methods used for risk classification are included in the reviewed documents.

In conclusion, in this area of scarce evidence and given the variability in the tissue-damage risk reported in the literature, the Delphi expert consensus methodology facilitates decision making when reviewing the different reference sources and allows the experience of the panellists to be included. In the final classification, for approximately 90% of the antineoplastics, the rate of consensus of the expert panel was above 85%; for 74% of the antineoplastics, consensus was 100%, and offered a solid ground for management decisions.

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Bibliography

1. National Cancer Institute. Common Terminology Criteria for Adverse Events. Version 5.0 (CTCAE) [monography at Internet]. US: Department of Health and Human Services. National Cancer Institute; 2017 [accessed 12/11/2020]. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11
2. Kreidieh FY, Moukadem HA, El Saghir NS. Overview, prevention and management of chemotherapy extravasation. World J Clin Oncol. 2016;7(1):87-97. DOI: 10.5306/wjco.v7.i1.87
3. Kimmel J, Fleming P, Cuellar S, Anderson J, Haaf CM. Pharmacological management of anticancer agent extravasation: A single institutional guideline. J Oncol Pharm Pract. 2018;24(2):129-38. DOI: 10.1177/1078155217690924
4. British Columbia Cancer Agency. Prevention and management of extravasation of chemotherapy [monography at Internet]. Canadá: British Columbia Cancer Agency; 2016 [accessed 10/01/2020]. Available at: http://www.bccancer.bc.ca/systemic-therapy-site/Documents/Policy%20and%20Forms/III_20_ExtravasationManagement.pdf

5. Cancer Institute New South Wales (NSW). Extravasation Management V.4 [monography at Internet]. Australia: Cancer Institute New South Wales; 2019 [accessed 12/16/2020]. Available at: https://www.eviq.org.au/clinical-resources/extravasation/157-extravasation-management
6. West of Scotland Cancer Network (WoSCAN) Cancer Nursing and Pharmacy Group. Chemotherapy extravasation guideline [monography at Internet]. Scotland: West of Scotland Cancer Network; 2009 [accessed 12/10/2020]. Available at: https://pdf4pro.com/view/chemotherapy-extravasation-guideline-2a98fa.html
7. Smolders EJ, Benoist GE, Smit CCH, Ter Horst P. An update on extravasation: basic knowledge for clinical pharmacists. Eur J Hosp Pharm. (pendiente de publicación, aceptado abril 2020). DOI: 10.1136/ejhpharm-2019-002152
8. Mader I, Fürst-Weger PR, Mader RM, Nogler-Semenitz E, Wassertheurer S. Extravasation of cytotoxic agents; Compendium for Prevention and Management. 2ª ed. Austria: Springer-Verlag; 2010.
9. Mouridsen HT, Langer SW, Buter J, Eidtmann H, Rosti G, de Wit M, *et al.* Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. Ann Oncol. 2007;18(3):546-50. DOI: 10.1093/annonc/mdl413
10. Valera-Ruiz M, Díaz-Bravo L, García-Durán. Descripción y usos del método Delphi en investigaciones del área de la salud. Inv Ed Med. 2012; 1(2):90-5.
11. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm. 2016;38(3):655-62. DOI: 10.1007/s11096-016-0257-x
12. Haines ST, Haines SL, MacLaughlin EJ, Van Amburgh JA. Recommendations for Evaluating Practice-Related Activities of Pharmacy Faculty: A Delphi Consensus. Ann Pharmacother. 2017;51(4):345-53. DOI: 10.1177/1060028016683496
13. Monje-Agudo P, Borrego-Izquierdo Y, Robustillo-Cortés ML, Jiménez-Galán R, Almeida-González CV, Morillo-Verdugo RA. Diseño y validación de una encuesta de satisfacción con la atención farmacéutica recibida en las consultas de farmacia hospitalaria. Farm Hosp. 2015;39(3):152-6. DOI: 10.7399/fh.2015.39.3.8366
14. Morillo Verdugo R, Villarreal Arévalo AL, Álvarez De Sotomayor M, Robustillo Cortés ML. Desarrollo de una taxonomía de las intervenciones farmacéuticas en pacientes VIH+ basados en el modelo CMO. Farm Hosp. 2016;40(6):544-68. DOI: 10.7399/fh.2016.40.6.10567
15. Covvey JR, Ryan M. Use of a Modified Delphi Process to Determine Course Objectives for a Model Global Health Course in a Pharmacy Curriculum. Am J Pharm Educ. 2018;82(8):973-82. DOI: 10.5688/ajpe6358
16. Gutiérrez-Urbón JM, Gil-Navarro MV, Moreno-Ramos F, Núñez-Núñez M, Paño-Pardo JR, Periáñez-Párraga L. Indicadores del uso hospitalario de antimicrobianos basados en el consumo. Farm Hosp. 2019;43(3):94-100. DOI: 10.7399/fh.11163
17. Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. Ann Oncol. 2012;23(Supl 7):vii167-73. DOI: 10.1093/annonc/mds294
18. Conde-Estévez D, Mateu-de Antonio J. Actualización del manejo de extravasaciones de agentes citostáticos. Farm Hosp. 2012;36(1):34-42. DOI: 10.1016/j.farma.2011.01.002
19. West Midlands Expert Advisory Group for Systemic Anti-Cancer Therapy (SACT). Guidelines for the Management of Extravasation of a Systemic Anti-Cancer Therapy including Cytotoxic Agents [monography at Internet]. England: National Health System; 2017 [accessed 12/10/2020]. Available at: https://www.england.nhs.uk/midlands/wp-content/uploads/sites/46/2019/05/management-extravasation-of-a-systemic-anti-cancer-therapy-including-cytotoxic-agents.pdf
20. Buter J, Steele KT, Chung KC, Elzinga K. Extravasation injury from chemotherapy and other non-antineoplastic vesicants. En: Saravese DMF, Collins KA (eds.) [monography at Internet]. US: UpToDate, Waltham, MA; 2020 [accessed 12/17/2020]. Available at: https://www.uptodate.com/contents/extravasation-injury-from-chemotherapy-and-other-non-antineoplastic-vesicants?search=extravasation&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
21. Extravasation. Drug consult [monography at Internet]. Greenwood Village (CO): IBM Corporation; 2016 [accessed 12/10/2020]. Available at: https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true/CS/C24516/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/D4A3E7/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=1481&contentSetId=50
22. Albert-Marí A, Díaz-Carrasco MS, Cercós-Lleti AC, Conde-Estévez D, Esteban-Mensua MJ, Gil-Lemus MA, *et al.* Monografía Prevención y tratamiento de extravasaciones de fármacos antineoplásicos. Grupo GEDEFO-SEFH [monography at Internet]. Madrid: SEFH; 2020 [accessed 12/10/2020]. Available at: http://gruposdetrabajo.sefh.es/gedefo/index.php/monografia-de-extravasaciones
23. Sconfienza LM, Adriaensen M, Albano D, Aparisi Gómez MP, Bazzocchi A, Beggs I, *et al.* Clinical indications for image-guided interventional procedures in the musculoskeletal system: a Delphi-based consensus paper from the European Society of Musculoskeletal Radiology (ESSR)-Part II, elbow and wrist. Eur Radiol. 2020;30(4):2220-30. DOI: 10.1007/s00330-019-06545-6
24. Janke KK, Kelley KA, Sweet BV, Kuba SE. A Modified Delphi Process to Define Competencies for Assessment Leads Supporting a Doctor of Pharmacy Program. Am J Pharm Educ. 2016;80(10):1-8. DOI: 10.5688/ajpe8010167
25. Ignoffo R, Chan L, Knapp K, Chan E, Ip E, Bandy J, *et al.* Efficient and effective precepting of pharmacy students in acute and ambulatory care rotations: A Delphi expert panel study. Am J Health Syst Pharm. 2017;74(19):1570-8. DOI: 10.2146/ajhp170181
26. Jorm AF. Using the Delphi expert consensus method in mental health research. Aust N Z J Psychiatry. 2015;49(10):887-97. DOI: 10.1177/0004867415600891
27. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS One. 2011;6(6):1-8. DOI: 10.1371/journal.pone.0020476
28. National Comprehensive Cancer Network (NCCN). NCCN Categories of Evidence and Consensus [monography at Internet]. Jenkintown, PA: National Comprehensive Cancer Network; 2017 [accessed 12/12/2020]. Available at: https://www.nccn.org/professionals/physician_gls/categories_of_consensus.aspx
29. Gilbar PJ, Carrington CV. The incidence of extravasation of vinca alkaloids supplied in syringes or mini-bags. J Oncol Pharm Pract. 2006;12(2):113-8. DOI: 10.1177/1078155206070448