Reviewed by 00209021

Manuscript Number	21679
Manuscript Title	Overview, Prevention and Management of Chemotherapy Extravasation
Review Time	2015-08-21 15:25

Comments To Authors

Well written manuscript summarizing the clinical aspects and management of extravasation and deserves publication. Minor concerns related to manuscript are below:

Thank you for your comment

-1. Evidence levels could be given in a different table or under the table 3 as footnote to ease reading.

Please note that we have split table 3 into two tables 4 and 5 as suggested.

2. References are not sutiable with the journal's style (number of authors, PMID and DOI numbers).

We looked at WJCO instructions to authors, in addition to recently published articles, and adjusted our references accordingly. We added PubMed and DOI, where available.

3. The description of grade 1 in table 1? (what does the blank mean?)

We left grade 1 blank because the grading of extravasation starts with minimum grade 2 up to maximum grade 5 according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.

4. Table 2 summarizes which guidelines? (related refereces could be inserted into the table)

Table 2 (now table 3) is a summary of all guidelines mentioned in the section named “Prevention”. We added related references in the table in track changes.

5. Evidence levels belong to which references in table 3?

Table 3 is now tables 4 and 5. References for the evidence levels were provided in the text. We added them in the tables (Ref 16).

Classification	○ Grade A (Excellent) ◉ Grade B (Very good) ○ Grade C (Good) ○ Grade D (Fair) ○ Grade E (Poor)
Language evaluation	◉ Grade A: priority publishing ○ Grade B: minor language polishing ○ Grade C: a great deal of language polishing ○ Grade D: rejected
Conclusion	○ Accept ○ High priority for publication ○ Rejection ◉ Minor revision ○ Major revision
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Reviewed by 03087211

Manuscript Number	21679
Manuscript Title	Overview, Prevention and Management of Chemotherapy Extravasation
Review Time	2015-07-29 01:07

Comments To Authors

The work is interesting but I have the following suggestions. 1. English should be improved throughout the manuscript.

Thank you. Few proof reading changes were done.

2. Abstract should be provided with quantitative information.

Thank you for your comment. Please find below an updated expanded version of the abstract based on the body of the manuscript;

Chemotherapy extravasation remains a preventable accidental complication of chemotherapy administration and may result in serious damage to patients. It still has a prevalence that ranges from 0.1 to 6% when administered through a peripheral intravenous access and from 0.26 to 4.7% when administered through a central venous access device. We review in this article the clinical aspects of chemotherapy extravasation and latest advances in definitions, classification, prevention, management and guidelines.

Intravenously administered chemotherapeutic drugs are classified according to the agents' damage potential. Chemotherapy extravasation is graded according to tissue damage as grade 2 (erythema with associated symptoms of edema, pain, induration and phlebitis), grade 3 (ulceration and necrosis), grade 4 (life-threatening consequences requiring urgent intervention), and grade 5 (extravasation that leads to death).

Management of extravasation includes non-pharmacological methods such as site irrigation, and pharmacological methods such as dexrazoxane, hyaluronidase, dimethyl sulfoxide (DMSO), sodium thiosulfate according to the extravasated agent, and possible surgical debridement and skin grafting. DMSO is an organosulfar solvent that is applied topically to improve absorption of the extravasated solvent. Dexrazoxane is an iron chelator that has been shown to prevent and/or reduce tissue damage after anthracyclines extravasation when given within 6 hours and repeated at 24 and 48 hours.

Prevention is most essential and includes staff education, appropriate selection of vascular access, and monitoring of infusion site. We stress the importance of education and training of the oncology team and the availability of new

antidotes like dexrazoxane wherever anthracyclines are being used.

3. Introduction is not complete and a paragraph should be added on cancer scenario and natural products with the citation of the following references. -Heterocyclic Scaffolds: Centrality in Anticancer Drug Development, Curr. Drug Target, In Press (2015). -Glutamic acid and its derivatives: Candidates for rational design of anticancer drugs, Future Med. Chem., 5, 961-978 (2013). -Curcumin-I Knoevenagel's condensates and their Schiff's bases as anticancer agents: Synthesis, pharmacological and simulation studies, Bioorg. & Med. Chem., 21: 3808-3820 (2013). -Platinum Compounds: A hope for future cancer chemotherapy, Anti-Cancer Agents Med. Chem., 13: 296-306 (2013). -Thalidomide: A Banned Drug Resurged into Future Anticancer Drug, Current Drug Ther, 7: 13-23 (2012). -Cancer Scenario in India with Future Perspectives, Cancer Therapy, 8: 56-70 (2011). -Social aspects of cancer genesis, Can. Ther., 8: 6-14 (2011). Imran Ali, Nano anti-cancer drugs: Pros and cons and future perspectives, Current Cancer Drug Targets, 11, 131-134 (2011). -Advances in nano drugs for cancer chemotherapy, Current Cancer Drug Targets, 11, 135-146 (2011). -Natural Products: Human Friendly Anti-Cancer Medications, Egyp. Pharm. J., 9: 133-179 (2010).

Thank you. We added a paragraph under "Use of biologically synthesized nanoparticles" as shown below:**Use of biologically synthesized nanoparticles**

Recent advances in the development of chemotherapeutic agents that incorporates biologically synthesized nanoparticles have been associated with less toxicity to surrounding tissue (31). Nanodrugs are based on the combination of chemotherapeutic molecules with nanoparticles carriers, which include liposome, polymer, and micelle (68). Chemotherapeutic molecules which have been used so far for synthesis of nanoparticles include cisplatin, carboplatin, doxorubicin, 5-fluorouracil, paclitaxel, vinblastin and etoposide (71). For example, the use of liposomal forms of chemotherapeutic agents such as doxorubicin was associated with decreased diffusion capacity of the drug and hence less toxicity to surrounding tissue (31, 71)...

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Language evaluation	○ Grade A: priority publishing ○ Grade B: minor language polishing ◉ Grade C: a great deal of language polishing ○ Grade D: rejected
Conclusion	○ Accept ○ High priority for publication ○ Rejection ◉ Minor revision ○ Major revision
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Comments To Authors	

Dear Dr. El Saghir,

Here is the third comments about the manuscript No. 21679. And the director will give first decision soon, please wait.

Comments: I consider the manuscript should be accepted with minor revision

This is a review about an unfrequent subject which is chemotherapy extravasation.

The manuscript has several strong points:
- The scarce number of reviews of this subject in the literature increase the value of an updated manuscript.
-The method of review is well described and it is appropriate
- The review is well written and easy readible.
- The manuscript deals with the most relevant issues in chemotherapy extravasation including prevention, non-pharmacological and pharmacological measures and even experimental methods.
- The references are quite updated.

However I consider that there are some points that could be improved.
- In reference to the DMSO management, the authors does not cited the manuscript in which the recommendation is based (Bertelli et al. J Clin Oncol 1995) this is an important reference in this context as it is one of the few prospective studies in this field. Moreover I would recommend to discuss in some lines the most relevant points of this paper such as patients included in the study and drugs extravasated treated with DMSO.

Thank you for your suggestion. We added text and reference of the article by Bertelli et al as shown below:

DMSO is an organosulfar solvent that is topically applied to improve absorption of the extravasated solvent(21, 49). It also has free-radical scavenging properties(3). Its efficacy was observed in few studies. In a prospective study by Cassagnol et al, patients with anthracycline extravasation, DMSO 99% was administered twice daily for a period of 14 days and no ulcers were described(3) . In another prospective study by Bertelli et al, out of a total of 122 assessable patients with extravasation of doxorubicin, epirubicin, mitomycin, mitoxantrone, cisplatin,

carboplatin, ifosfamide or fluorouracil, only one patient suffered an ulceration. Treatment with DMSO was generally well tolerated with the only side effect being mild local burning and breath odor(58). The use of topical DMSO (99%) as an antidote to anthracycline extravasation and to Mytomicin C has level **IV-B** evidence (Evidence Level IV: Evidence from well-designed case-control and cohort; "B": moderate strength of recommendation)(16, 55). DMSO is available as a solvent, and a dropper is usually used to instill drops over the affected skin.It is used asa topical application of DMSO 99% of four drops per 10 cm2 to twice the size of the extravasation area(3, 22). In cases of anthracyclines extravasation, the combination of DMSO and cooling are most commonly described initial therapy for minor anthracyclines extravasation, especially when dexrazoxane is not available.

-Regarding the chapter about dexrazoxane I would recommend to discuss in dept the two prospective trials that lead to approval of this drug (Mouridsen et al Ann Oncol 2007, already cited by the authors)

Thank you for your comment. More information was added regarding this paper by Mouridsen et al.

The two prospective open-label single-arm studies in patients with anthracyclines extravasation were published in 2007 by Mouridsen et al(30). Dexrazoxane was given within 6 hours and repeated at 24 and 48 hours. Efficacy was noted in 53 of 54 patients (98.2%) and only one patient required surgical debridement. Toxicity was manageable and includes transient elevation of liver enzymes and neutropenia that may be also due to chemotherapy itself.

- I would recommend as well to include a table with the different type of drugs classified according to its vesicant potential.

Thank you. Table 1 was added.

- Regarding the grades of severitiy according to CTCAE I find that the text and the table are somehow repetitive, I would recommend to include only one mention to this point (table 1 or preious text explaining the different grades)

Thank you for your comment. We referred the reader in the text to the table 2 (initially table 1) as shown in the text in track changes.

-Finally I consider that including a chapter (or a short recommendation) about

specific measures in case of central device extravasation would increase the value of the review (ESMO guidelines include some guidelines in this context).

We have included the following section regarding extravasation in case of central venous access devices and included ESMO guidelines in this context, in addition to a recently published article in the European Journal of Surgical Oncology.

Extravasation in the presence of central venous access devices

Accidental cases of extravasation in the presence of central venous access devices is very rare and reported in 0.24% of cases (65). Extravasation may occur in the subcutaneous tissue of the chest wall or neck, or in the mediastinum. Physicians and nurses should make sure that infusion needles are properly inserted in the port or chamber. In cases of extravasation in the subcutaneous tissue, infusion should be stopped immediately when patient complains of pain or swelling. Pharmacological management, including the use of dexrazoxane for anthracyclines extravasation should be instituted as reviewed in the above sections (65). A recent report indicated benefit from immediate removal of the central venous access device along with Subcutaneous Wash-Out Procedure (SWOP) if extravasation is detected early, to help minimize the exposure of tissue to extravasated agent and the risk of tissue necrosis (66).In cases of mediatinal extravasation, ESMO guidelines include stopping the infusion, use of dexrazoxane for cases of anthracyclines, and possible surgical draining procedures for the remaining solution, antibiotics, steroids and analgesics to control symptoms from mediastinitis or pleuritic (66).