BLOOD

# Antidotes to Vesicant Chemotherapy Extravasations

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The extravasation of vesicant cancer chemotherapeutic agents remains one of the single most distressing complications that hematologists and oncologists face. Vesicant agents, or drugs that cause ulceration upon direct tissue contact, are among the most frequently used compounds in clinical cancer chemotherapy. The list of vesicant drugs includes anthracyclines such as doxorubicin,[1–9] daunorubicin[9–13] and other DNA intercalators,[14,15] alkylating agents such as nitrogen mustard[18,19] and mitomycin C[20–22] and the plant alkaloids, vincristine and vinblastine.[23] Table 1 identifies the cancer chemotherapeutic drugs that can produce soft tissue ulceration upon extravasation. Antidotes have been proposed for many of these agents.

Besides the pharmacologic treatment of vesicant extravasations, a variety of non-pharmacologic approaches must be considered. First and foremost among these is prevention. In this regard, it is clear that the utmost caution must be placed on the careful administration of these medications. One important means of preventing vesicant extravasations has been the development of subcutaneous indwelling vascular access devices. However, despite the advent and extensive use of these vascular access devices, drug extravasation continues to be a problem.

## Vascular Access Devices

In a review of 329 procedures using vascular devices in over 300 patients, an extravasation incidence of 6.4% was reported.[54] This is similar to the reported incidence of doxorubicin extravasation of 6.5% when peripheral venipuncture techniques are used.[3] Reed et al have also reported drug extravasation from venous access devices and surprisingly in 1 case, severe skin necrosis from the antimetabolite fluorouracil was described.[48] One mechanism for this type of extravasation injury can involve retrograde subcutaneous leakage from percutaneously inserted catheters clogged by a fibrin sheath.[55] In addition, indwelling catheters from subcutaneous reservoirs can also spontaneously retract from the subclavian vein.[56] Thus, even with the best techniques, and the use of indwelling access devices, chemotherapy extravasation has not been eliminated.

## Surgery to Remove Trapped Drug

Once an extravasation has occurred, it is imperative to terminate the infusion of the medication and evaluate the site for potential definitive treatment. Oftentimes, serious extravasations will require surgical excision of the tissue and this should not be delayed.[57–60] One cogent reason for rapid evaluation for potential surgery is exemplified by extravasations of doxorubicin. This agent can be trapped in skin tissues for several months following a serious extravasation[61–63] (Table 2). In these cases it is hypothesized that active drug is sequentially released from dying cells and is taken up again by adjacent healthy cells. This would explain the prolonged retention of doxorubicin in skin and underlying soft tissues.[61] The results in the Figure show that following an extravasation doxorubicin can be partially metabolized to doxorubicinol and/or to the inactive aglycone in skin tissues.

One of the best clinical indicators of the need for

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**Table 1** Propensity for cancer drugs to product necrosis upon inadvertant extravasation

| High | Low | None |
|---|---|---|
| *DNA intercalators* | | |
| Doxorubicin[1–9] | Liposomal anthracyclines[24,25] | Mithramycin[26] |
| Daunorubicin[9–13] | Mitoxantrone[27–31]* | |
| Dactinomycin[14,17] | Esorubicin[34–36] | |
| Epirubicin[8,32,33] | Menogaril[40,41]† | |
| Bisantrene[37–39] | Aclacinomycin[8] | |
| Cyanomorpholinyl doxorubicin[42] | | |
| Amsacrine[26] | | |
| *Alkylating or DNA-binding agents* | | |
| Mechloroethamine[18,19] | Cisplatin[17,27,43–45] | Melphalan[27] |
| Mitomycin C[20–22] | | Carmustine |
| | | Dacarbazine[46]† |
| *Antimetabolites* | | |
| — | Fluorouracil[47–49]*,† | Cytarbine |
| | | Methotrexate |
| *Plant products* | | |
| Vincristine[23,50] | — | Teniposide[51]† |
| Vinblastine[23,52] | Etoposide[8,9,51]† | |
| Vindesine[8,23,53] | | |
| *Miscellaneous* | | |
| — | Bleomycin[8,49]† | L-Asparaginase |
| *Biologicals* | | |
| — | | α-Interferon |
| | | Interleukin-2† |
| | | Tumor necrosis factor† |

* Very rare reports of clinical soft tissue ulceration following extravasation.
† Occasionally causes local phlebitis and soft tissue irritation but usually not ulceration.

**Table 2** Experimental doxorubicin extravasation treatment studies

| *Agents* | *Effective* | Ineffective |
|---|---|---|
| Glucocorticosteroids | Mice[72] | Rabbits[70,78] |
| | Rats[74,75] | Rats[58] |
| | | Mice[71] |
| | | Guinea Pig[73] |
| Dimethylsulfoxide | Rats[85] | Mice[86] |
| Vitamin E | Pigs[99] | Rabbits[70] |
| | Guinea Pig[100] | Pigs[101,102] |
| | | Rats[58] |
| Sodium bicarbonate | Rats[77] | Rabbits[70,78,79] |
| | | Mice[72] |
| | | Rats[75] |
| Radical dimer ($DHM_3$) | Pigs[95,96] | |
| Saline | | Mice[72,91] |
| | | Rats[58] |
| Beta-adrenergics | Mice[91] | |
| | Rats[74] | |
| Antioxidants | | |
| (e.g. BHT) | Mice[88] | |
| | Rats[75] | |
| Antihistamines | | Mice[91] |
| Hyaluronidase | | Mice[71,97] |
| *Non-pharmacologic procedures* | | |
| Topical heating | | Mice[108] |
| Topical cooling | Mice[108] | Rats[75] |
| | Pigs[102] | |
| Surgical excission | Rats[58–60,69] | |

subsequent surgery is reported to be pain at the site of the extravasation 1–2 weeks following the event.[57] When surgery is indicated, a wide excision of the tissues is necessary to completely remove non-viable tissues and any locally trapped drug.[6,57,60] Because of the very prolonged evolution of anthracycline extravasation injuries, it is advisable that surgical consultation not be delayed so that large tissue areas may be spared subsequent drug exposure.[57,60] In contrast, if an open ulcer is allowed to develop, the area of excision may need to be quite large and may involve deep structures such as nerves and tendons.[1,2]

## Interpreting Pharmacologic Treatment Reports

Because of the severity of the ulcers which develop and the need for extensive local surgery to control evolving ulcerations, a variety of pharmacologic antidotes have been postulated to prevent the development of this serious complication.[64] Oftentimes, putative antidotes have been reported in clinical anecdotes which, while helpful, do not have the rigorous controls needed for an unequivocal test of efficacy. Secondly, as Larson has shown, only about one third of known vesicant extravasations will produce ulcers when conservative local management is used (ice and elevation of the effected limb).[57] This means that there is a high likelihood of overestimating the true efficacy of a putative local antidote since the majority of patients will have a good outcome following a vesicant extravasation with only conservative therapy.

In the following sections a variety of pharmacologic approaches to extravasation management are reviewed for different vesicant cancer chemotherapeutic agents. In each case, both clinical and experimental studies are analyzed with the intent to provide a comprehensive survey of this important area of cancer drug toxicity.

## Doxorubicin Extravasations

Doxorubicin extravasations are reported to occur in up to 6% of patients given the drug by peripheral

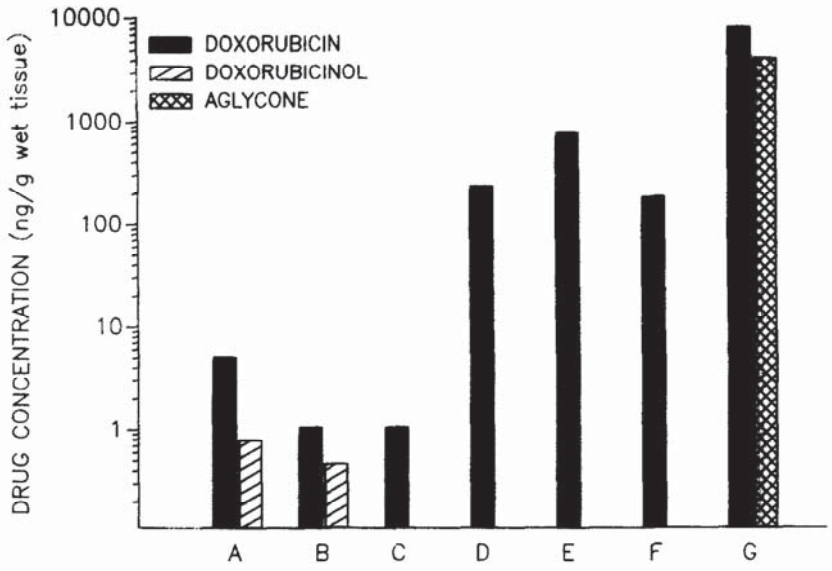


**Figure** A comparison of doxorubicin, doxorubicinol or doxorubicin aglycone levels in human skin and soft tissues excised from extravasation sites 5 ½ months after extravasation of 24 mg.[61] (two dermis specimens, A and B); 1 month after an extravasation of 15 mg[61] (dermis specimen C); 1 week after extravasation of 8 mg (subcutaneous tissue specimen D); 28 days after extravasation of an unknown amount of a 5 mg/ml solution[62] (specimens E, [central ulcer] and F [peripheral ulcer area]) and 2 weeks after extravasation of an unknown amount of 2.1 mg/ml solution[63] (central ulcer area composed of fat and muscle tissue, G).

venous injection.[3] A much more realistic figure is the 0.5% incidence described by Laughlin et al.[5] Perhaps the most common local complication from doxorubicin administration is not extravasation but the occurrence of a venous flare reaction.[65–67] It is characterized by local edema, venous streaking and pruritus over the area of the injection site. This reportedly occurs in up to 3% of injections[67] and generally has a benign outcome. Corticosteroids and antihistamines are frequently used either prophylactically or to treat a fulminant reaction with equivocal results.

For the more serious extravasation injuries, the typical hallmark is pain and swelling at the injection site which is usually quite severe and is not generally delayed.[1–8] Attendant with this symptomatology is the inability to obtain a blood return from the site.[3] In this setting it is imperative that the administration of any remaining doxorubicin solution be discontinued. While it is recommended to try to leave the needle in place to evacuate extravasated material this is generally not productive due to tissue blockage at the needle terminus. Nevertheless, this procedure should be attempted since occasionally, large amounts of extravasated fluid containing drug can be recovered.[8,39] Following attempted evacuation of locally extravasated doxorubicin solution, the clinician is left with a variety of options for local treatment.

## Doxorubicin Antidotes

### *Glucocorticosteroids*

Glucocorticosteroids, such as hydrocortisone, have been advocated as local anthracycline antidotes in a number of clinical reports.[1–3] The underlying pharmacologic consideration for the use of glucocorticosteroids is that some component of doxorubicin extravasation injury involves acute inflammation. However, in a rabbit model Luedke et al were not able to demonstrate a significant acute inflammatory reaction in response to ulcerogenic doses of doxorubicin given intradermally.[68] In contrast, in the subcutaneous rat model, Rudolph et al did describe a delayed acute inflammatory response in histological sections of skin obtained 1 week following subcutaneous administration of doxorubicin.[69] Clearly though, the majority of doxorubicin soft tissue damage appears to be mediated by direct necrosis. Thus, there is not a confirmed histopathologic rationale for glucocorticosteroid use in treating doxorubicin extravasations. Despite these considerations, glucocorticosteroids have long been used in the treatment of doxorubicin extravasations.

### *Clinical Cases*

Reilly et al published an analysis of 10 patients experiencing doxorubicin extravasation.[2] Three patients were treated with 100 mg of hydrocortisone and ulceration occurred in only 1 patient. All of these extravasations occurred on the forearm. In a detailed nursing study by Barlock et al, hydrocortisone was given by 2 methods to 9 patients experiencing a doxorubicin extravasation.[3] Importantly, local ice packs were also used following these hydrocortisone treatments. No ulcers occurred in any of the 9 patients treated with hydrocortisone and ice. However, the 100 mg hydrocortisone sodium succinate injections used in this study did not prevent pain, erythema, a loss of vein patency and a limited range of motion in 5 of the 9 patients. Three of these latter 5 patients received second intra-

dermal or subcutaneous hydrocortisone injections around the site for 1–7 days after the extravasation. While this seemed to alleviate some symptoms, it did not restore vein patency. Another 4 patients in this series were treated with multiple I.D. and S.Q. injections of hydrocortisone (50–200 mg total) and had no local complications. A 1% hydrocortisone cream was also applied to the site in these patients twice daily until erythema disappeared. Vein patency was preserved in these patients and the only residual symptoms involved mild tenderness and a brownish skin discoloration which slowly resolved.[3] Thus, aggressive hydrocortisone treatments appeared to be effective in this small clinical series.

The limited number of patients studied and the uncontrolled nature of the extravasation event makes this report difficult to evaluate. It should also be emphasized again that only one third of clinical vesicant extravasations may be expected to produce ulcers when conservative (non-pharmacologic) management is used.[57] Thus, it is unclear if the use of hydrocortisone truly impacts on the evolution of ulcers following doxorubicin extravasation. However, the lack of ulceration in the 9 patients reported by Barlock does suggest some antidotal activity for local hydrocortisone.[3]

*Experimental Studies*

In contrast to the paucity of clinical doxorubicin extravasation cases treated with glucocorticosteroids, a large number of experimental studies are available wherein topical or locally injected corticosteroids have been tested. In New Zealand rabbits, the potent fluorinated corticosteroid triamcinolone (10 mg/ml) was not able to block subcutaneous doxorubicin ulceration.[70] Similarly, CDF mice given 0.25 mg of subcutaneous doxorubicin were not protected from ulceration by doses of 5–50 mg of hydrocortisone sodium succinate or 1 mg of dexamethasone.[71] In another study using dehaired BALB/c mice, a large intradermal hydrocortisone dose of 12.5 mg actually increased doxorubicin ulceration.[72] A lower 'intermediate' hydrocortisone dose of 6.25 mg was ineffective, but a 'low' 2.5 mg dose partially blocked doxorubicin skin ulceration.[72] In this same study, neither intramuscular hydrocortisone nor daily topical 0.5% hydrocortisone cream applications blocked doxorubicin-induced skin ulcers.[72] Another trial studied guinea pigs given intradermal doxorubicin. These animals also were not protected from skin ulceration by either intradermal or subcutaneous hydrocortisone used at several unspecified concentrations.[73]

In contrast, a preliminary study performed in rats and mice at Adria Laboratories showed a beneficial effect for 0.6 mg of betamethasone (20 mg hydrocortisone equivalent).[74] But in another study, a lower dose of 0.2 mg of hydrocortisone was ineffective in rats given intradermal doxorubicin.[58] In Sprague-Dawley rats it was reported that a minor reduction in doxorubicin ulceration was produced by 5 mg of intradermal hydrocortisone.[75] Of interest, this study also showed that multiple hydrocortisone injections were *not* more beneficial than a single injection. Indeed, the multiple injection hydrocortisone regimen actually deepened skin ulcers produced by doxorubicin.[75] In a final study, hydrocortisone was shown to be ineffective against doxorubicin ulceration in rats although early surgical excision was highly effective at decreasing ulcer size and enhancing ulcer healing.[60]

These 7 experimental studies describe inconsistent antidotal activity for hydrocortisone as a local doxorubicin extravasation antidote: 3 reports describe moderate ulcer size reduction with glucocorticosteroids;[72,74,75] and 5 reports describe no antidotal effects.[58,70–73] Conversely, when very high doses are used[72] or multiple injections are given,[75] hydrocortisone can significantly increase doxorubicin ulcer sizes in these experimental settings. In addition, since the histopathologic studies of doxorubicin skin ulcers do not describe acute inflammation,[68] the pharmacologic rationale for glucocorticosteroid use is unclear. Despite this, hydrocortisone is still suggested as a local remedy in the package insert for Adriamycin$^{R}$ (Adria Laboratories, Columbus) and low hydrocortisone doses given by a single injection, should not increase doxorubicin soft tissue damage. Furthermore, hydrocortisone is frequently recommended as a treatment for doxorubicin-induced venous flare reactions which are probably much more common than extravasations.[67] Thus, hydrocortisone may be a useful agent to have on hand during doxorubicin administration but its role as a direct doxorubicin extravasation antidote is not established.

*Local pH Manipulations*

Considerable interest was generated by an anecdotal report of the successful treatment of doxorubicin extravasation (40 mg) using hydrocortisone plus 8.4% sodium bicarbonate (pH 8.15).[76] The rationale for this treatment has been reported to involve instability of the doxorubicin glycosidic bond at an alkaline pH. In one animal trial, Wistar rats receiving 0.6 mg doxorubicin intradermally were partially protected from ulceration by an immediate intradermal injection of 0.3 ml of 8.4% sodium bicarbonate solution.[77] In contrast, a large number of other experimental studies have described no antidotal efficacy for sodium bicarbonate as a doxorubicin antidote in mice,[72] rats,[52,58,62,70,75] rabbits[78] and guinea pigs.[73] In addition, one study has shown that doxorubicin ulcers in rats are consistently produced despite controlled manipulation of the drug's pH over the range of 5.5–8.0.[79] Furthermore, sodium bicarbonate is itself a known vesicant if extravasated.[80,81] In one report, 8 of 11 patients experiencing a bicarbonate extravasation required skin grafts to satisfactorily resolve large areas of soft tissue necrosis. Importantly, each of these cases involved the same 8.4%

solution of sodium bicarbonate as was recommended for treating doxorubicin extravasations.

*Hydrocortisone–Sodium Bicarbonate*

Sodium bicarbonate has been combined with hydrocortisone in 2 experimental studies. No antidotal effects were noted for this combination in rats[58,75] or in mice.[72] Indeed, in some studies there was evidence of enhanced doxorubicin skin tissue damage following the injection of hydrocortisone mixed with 8.4% sodium bicarbonate.[75]

The experimental studies and the clinical cases of severe bicarbonate extravasation injuries clearly discount any role for sodium bicarbonate as a doxorubicin antidote. This conclusion has recently been echoed in the oncology nursing literature.[82]

*Antioxidants*

Doxorubicin can produce oxygen free-radicals following enzyme-mediated redox cycling of the quinone moiety.[83] This is a postulated mechanism of cardiotoxicity for the drug[84] and similar oxidant effects could occur in doxorubicin-exposed skin tissues. Thus, a variety of antioxidants have been tested as local antidotes to doxorubicin skin extravasation. Svingen et al observed substantial antidotal activity for the combination of dimethylsulfoxide (DMSO) and alpha tocopherol (Vitamin E) in rat skin.[85] Vitamin E alone however, was found to be ineffective in experimental studies in mice[86] and rats.[51–53] DMSO will be reviewed in depth in a following section.

Butylated hydroxy toluene (BHT) is another potent antioxidant which is often added to foods and cooking oils to prevent oxidation (rancidity).[87] Daugherty et al were able to show significant reductions in doxorubicin ulcer size in mice given BHT.[88] The most effective BHT dose was 4 mg per mouse and both I.D. and topical routes of BHT administration were effective. In another study in rats, oral BHT prefeedings were able to reduce doxorubicin ulcer sizes.[75] This latter study also showed that hyperbaric oxygen and vitamin A did not significantly alter doxorubicin ulcer sizes but both BHT and another antioxidant, β-carotene, significantly blocked high dose doxorubicin lethality.[75]

These studies appear to rule out any antidotal efficacy for the antioxidant vitamins A and E. The consistent antidotal activity of BHT in the animal models does suggest that this antioxidant may be an effective antagonist to doxorubicin skin ulceration. However, in both positive studies, BHT did not completely prevent skin ulceration.

In a clinical trial, Ludwig et al have treated 6 anthracycline extravasations with dressings soaked in 90% DMSO and 10% alpha-tocopherol acetate (vitamin E).[89] These treatments were applied topically every 12 h for 2 days and no ulcers were observed. The only side-effect was local skin irritation under the dressings manifested by erythema and blisters in 2 patients. The erythema always resolved promptly after stopping the DMSO. In addition, an estimation of the amounts of drug extravasated in each case (about 3 mg) suggests that some local toxic effects would have occurred in the absence of the DMSO/vitamin E treatment.

*Beta-adrenergic Agents*

Pharmacologic studies in dogs have shown that doxorubicin releases endogenous histamine and catecholamines following intravenous administration.[90] These chemicals can then act as mediators of doxorubicin cardiotoxicity. In a mouse skin model, both propranolol and isoproterenol were shown to reduce doxorubicin skin ulceration. This effect appeared to be specific for $B_1$ receptors since it could not be reproduced with the $\beta_2$-specific agonist, terbutaline.[91] Isoproterenol was also effective in a rat skin toxicity model[74] and, propranolol has been shown to reduce doxorubicin uptake in isolated myocardial cells.[92] The reason for the effectiveness of opposing β-adrenergic agents in the mouse is unexplained and in some models, neither isoproterenol nor propranolol were effective.[58] This seems to discount a role for β-adrenergic agents as local doxorubicin extravasation antidotes.

Antihistamines also have not been effective as local antidotes to experimental doxorubicin skin ulcers including $H_1$ antihistamines such as diphenhydramine and the $H_2$ antihistamine cimetidine.[91] Because of the divergent findings with the β-adrenergics and the lack of efficacy for antihistamines, there does not appear to be any role for these agents in managing clinical doxorubicin extravasations.

*Radical Dimers*

Koch and coworkers have synthesized a series of oxomorpholinyl derivatives which can react with quinone-containing drugs to produce inactive byproducts.[93] These new compounds include the radical dimer bis(3,5–dimethyl–5–hydroxymethyl–2–oxomorpholin–3–yl) or DHM3 which reduces anthracyclines such as doxorubicin to insoluble (and inactive) 7–deoxyaglycone metabolites.[93] DHM3 has been shown to protect animals from acute doxorubicin lethality.[94,95] In addition, the radical dimer DHM3 has been injected into pigs given I.D. doxorubicin with significant (80%) reductions in the average size of skin ulcers.[95] In this study, a 10-fold molar ratio of DHM3:doxorubicin was required for maximally efficacy. Importantly, DHM3 alone was non-toxic in the I.D. pig skin model.[95]

In addition to doxorubicin, DHM3 can also reduce skin ulcers in pigs given other I.D. vesicants, including daunorubicin, menogaril, idarubicin, epirubicin, 5–iminodaunorubicin, aclarubicin and mitomycin

C.[96] DHM3 has also been shown to be effective against doxorubicin-induced skin ulcers in the mouse model (Dorr, unpublished observations). However, the radical dimer $DHM_3$ is not active against some vesicant drugs including vinblastine and mitoxantrone.

Mechanistic studies with anthracycline extravasations in pigs further suggest that skin toxicity with quinone-containing agents like doxorubicin may indeed be associated with the reductive formation of highly reactive quinone methide radicals at critical cellular sites of damage.[96] Thus, an agent such as DHM3 may rapidly reduce anthracyclines to inactive aglycones.[95] Cellular alkylation by quinone methides may explain the greater degree of skin toxicity seen with anthracyclines such as 5–iminodaunorubicin which do not form oxygen free-radicals, but which do form quinone-methide intermediates much more easily than other vesicant anthracyclines.[96]

These novel radical dimers have demonstrated consistent antidotal activity against experimental doxorubicin skin ulcers. They appear to produce little intrinsic toxicity. Importantly, unlike other 'antidotes', the radical dimers have a well defined specific mechanism of action, namely chemical reduction of vesicant quinone anticancer agents to inactive metabolites. DHM3 should be considered for immediate clinical testing as orphan drugs with indications in the emergency treatment of common vesicant extravasations.

### *Dimethylsulfoxide*

Dimethylsulfoxide (DMSO) has a number of biologic characteristics which make it an attractive potential local antidote to doxorubicin. First, DMSO is known to enhance skin permeability which might facilitate systemic absorption of an extravasated vesicant drug.[97] Second, DMSO has free-radical scavenging activities. This can prevent DNA damage from oxygen free-radicals which might be produced by drugs such as doxorubicin.[98] Several experimental and clinical trials have tested this hypothesis.

### *Experimental DMSO Studies*

Desai et al have reported complete protection against doxorubicin-induced skin ulcers using DMSO in both Sprague Dawley rats and in Yorkshire piglets.[99] DMSO was applied topically for 7 days (0.6 ml of a 100% solution). In this trial, topical DMSO also prevented ulcers from developing at distal, untreated doxorubicin injection sites. In another study using Sprague-Dawley rats, a combination of DMSO and 10% alpha-tocopherol decreased doxorubicin skin ulcers by almost 70%.[85] The maximally effective regimen involved topical administration of 0.1 ml of the vitamine E/DMSO mixture for 2 days. While alpha-tocopherol succinate was shown to be more active than the acetate or alcohol forms, no Vitamin E preparations were active in the absence of DMSO.[85] In guinea pigs, topical DMSO and 50% alpha-tocopherol were effective at reducing but not preventing I.D. doxorubicin skin ulcers.[100] The dose of doxorubicin was shown to be critical in this study since topical DMSO with alpha-tocopherol could not substantially reduce lesion sizes from doxorubicin doses greater than 0.05 mg.

In contrast to these studies, several negative trials of DMSO and/or alpha-tocopheryl are also reported. In the Yorkshire piglet, DMSO did not significantly reduce doxorubicin ulceration.[101] In this same study alpha-tocopherol (50 units I.D.) was shown to actually enhance doxorubicin skin ulcers. Similarly, Harwood et al could not demonstrate efficacy for a 7-day topical DMSO regimen as an antagonist to doxorubicin skin ulcers in pigs.[102] A 14-day topical DMSO regimen had limited efficacy but was inferior to simply cooling the site with ice.[102] Finally, no antidotal effects were noted in mice receiving topical DMSO and/or alpha-tocopherol in a mouse model.[86]

### *Clinical DMSO Reports*

The use of DMSO in the clinic has been described anecdotally in several cases in which different potential antidotes were combined. In 1 case, a 10 mg daunorubicin extravasation in a 42-year-old man was treated with sodium bicarbonate, dexamethasone (4 mg), ice packs and topical DMSO.[103] The DMSO regimen used 1.5 ml of a 70% solution which was applied to the site every 3–4 h for 10 days (a total dose of 90 ml). Pain relief and the prevention of ulcer formation were described for this patient. In another case, a 4–6 mg doxorubicin extravasation in a 49-year-old man was treated with 5 ml of 8.4% sodium bicarbonate, ice packs and DMSO (99%, analytical grade).[103] The DMSO was applied daily for 14 days and while ulceration did not occur, a $3 \times 2.5$ cm indurated area limiting elbow extension remained. Another patient treated with sodium bicarbonate, ice and DMSO had only residual pigmentation in the extravastion area with no functional impairment. In this trial the DMSO was applied every 6 hours for 1 week, then twice daily for another week. A similar outcome was described in a third patient receiving only ice and the identical DMSO regimen.[104]

These observations presaged a larger non-randomized clinical trial in 20 patients receiving topical DMSO for doxorubicin extravasations.[105] In this trial, 99% DMSO was applied twice to the apparent extravasation area, 6 times daily for 2 weeks. Doxorubicin (18 cases) or daunorubicin (2 cases) were the vesicant anthracyclines studied at 2 institutions. No open ulcers were described following DMSO treatment although initial swelling, erythema and pain were evident in 85%, 75% and 60% of this population, respectively. At least 3 months of follow-up were available for 16 patients and there were no symptoms in 6 (38%) and only pigmented induration in 10

(63%). DMSO toxicities primarily involved a transient burning sensation with urticaria and erythema during application. In addition, 6 patients described the characteristic garlic odor on their breath.

These results suggest that topical DMSO may have antidotal activity against anthracycline-induced skin ulceration. It is still unclear what pharmacologic mechanism is involved. The inactivity of DMSO in some studies using both rodents and pigs, cautions that DMSO's antidotal efficacy may be limited, or even artifactual. In this regard, the low degree of toxicity and the recently reported clinical trial clearly argue for broader studies of topical DMSO in treating anthracycline extravasations. However, the lack of a medically approved topical DMSO dosage form is a problem. Currently, only the formulation available is a 50% (vol/vol) DMSO solution in water. This product has an official indication limited to the intravesicular treatment of recurrent cystitis (Package Insert Rimso-50, Research Industries, Salt Lake City). This is unfortunate since the enhancement in percutaneous drug absorption by DMSO is only produced with highly concentrated DMSO solutions (generally >90%). Nonetheless, it is possible that DMSO may be acting as a vesicant antidote by other mechanisms such as free-radical scavenging or by anti-inflammatory or vasodilatory effects.[97] Certainly the most attractive hypothesis is enhanced percutaneous absorption of anthracyclines since it is known that anthracycline skin ulcers are associated with prolonged local drug retention.[61] Pharmacokinetic studies of doxorubicin disposition in skin tissues treated with topical DMSO could test this hypothesis and might additionally suggest better topical regimens for the clinic.

*Heat Versus Cold*

Chemical phlebitis is often managed by the application of warm compresses to the effected area. The rationale for this treatment involves increased blood flow to the area with a resultant enhanced resolution of pain and a resorption of local swelling. In contrast, topical cooling can act to shunt blood flow away from an area and reduce cellular metabolism. Local hypothermia is now well recognized as a technique to prevent doxorubicin-induced scalp alopecia in patients with solid tumors.[106,107] Thus, there are divergent rationale for the use of local heating or cooling to manage doxorubicin extravasations.

In a controlled trial of heating versus cooling in mice, topical skin cooling from a normal of 38°C to 17°C produced marked reductions in doxorubicin-induced ulceration.[108] In contrast, mild heating of the skin to 43–44°C resulted in a significant increase in doxorubicin-induced skin ulcers.[108] Indeed, the addition of heat to intradermal doxorubicin resulted in lethality from otherwise non-lethal doses of the drug.[108] Similar synergistic effects from heat and doxorubicin are also described in tumor cells.[108,109]

Importantly, these effects are not limited to the mouse model. In the pig, topical cooling was found to be much more effective than DMSO as a local doxorubicin extravasation antidote.[102] In addition, many of the 'positive' clinical anecdotes regarding doxorubicin extravasation management have involved the application of topical cooling with other agents.[2,57,102,104]

Topical cooling does not appear to reduce doxorubicin skin concentrations in vivo.[108] Rather, the antidotal effect may relate to critical phase transition states in cell membrane lipids.[110] For example, the in vitro studies have shown that tumor cell cytotoxicity from doxorubicin is markedly reduced when temperatures are less than 25°C. This effect appears to be due to a change in the fluidity of the plasma membrane rendering cells insensitive to doxorubicin lethality.[110] In summary, cooling clearly provides significant protection from doxorubicin cytotoxicity and this should comprise a mainstay of doxorubicin extravasation management.

**Daunorubicin**

Like doxorubicin, daunorubicin is a well known vesicant.[9–13,26] Most clinical reactions are noted by severe pain during the infusion of the drug.[9] Sometimes severe cellulitis is described in the absence of extravasation.[9] Neither dilution of the infusate nor the administration of heparin and hydrocortisone following daunorubicin have lessened this reaction.[12] In addition, daunorubicin has produced 1 case of severe necrosis of the hand following a retrograde distribution of drug through an arteriovenous fistula located in the forearm. Like doxorubicin, severe daunorubicin lesions require surgical excission to remove non-viable tissues and any locally entrapped drug.

In animal trials daunorubicin also produces dose-dependent skin ulcers.[12,26] The guinea pig model showed that daunomycin was a more potent vesicant than doxorubicin although a similar histologic pattern (necrosis and inflammation without granulation) was apparent.[12] The same enhanced potency for daunomycin over doxorubicin was also seen in the mouse model.[26] In the mouse model only DMSO appeared marginally effective as a daunorubicin antidote.[26] Ineffective daunorubicin 'antidotes' in the mouse skin model include sodium bicarbonate, heparin, hyaluronidase, cooling and isoproterenol.[26] As with doxorubicin, heating increased ulceration and this is compatible with synergistic effects noted in daunorubicin tumor cell cytotoxicity assays.[109]

**Epirubicin**

This anthracycline is the 4'hydroxyl epimer of doxorubicin. It has more potent antitumor effects than the parent compound on a weight basis[111] and may produce less cardiotoxicity at equimyelotoxic

doses.[111] In one phase II trial, 4% of patients developed chemical phlebitis.[112] Local pain and erythema without necrosis was described in another patient who experienced an epirubicin extravasation. The one reported case of extravasation necrosis for epirubicin[8] suggests that the drug may have a vesicant potency similar to its close chemical congener, doxorubicin.

### Idarubicin

Idarubicin is the 4-demethoxy derivative of daunorubicin. Like other second generation anthracyclines, this drug has greater antitumor potency than the parent compound but a qualitatively similar toxicity spectrum.[113] Idarubicin is more rapidly converted to the 13–dihydro (alcohol) metabolite than is either doxorubicin or daunorubicin and in addition, has some activity when administered orally.[113] Some idarubicin skin reactions have been reported in humans. In one trial, 2 patients experienced 'minimal' idarubicin extravasations which caused local pain, swelling and some necrosis.[114] Skin grafting was not required in these instances. These 2 experiences represented 2% of the evaluable drug administration courses.[114] No reports describing local antidotes to idarubicin extravasations are available, although the drug clearly has vesicant properties.

### Esorubicin

Esorubicin is the 4'deoxy analog of doxorubicin. Like epirubicin, this analog has increased cytotoxic potency and a similar range of clinical toxicities. Phlebitis, associated with erythema and itching, is more prominent with esorubicin. In one trial, 22% of patients experienced this local venous reaction.[115] Upon repeat drug administration, corticosteroids and diphenhydramine were unable to block this reaction which, nonetheless, was felt to be due to local histamine release.[33] A similar acute venous syndrome has been described by other groups using esorubicin.[116–118]

Experimentally esorubicin produces dose-dependent skin ulcers in mice given intradermal doses ranging from 0.2 to 0.5 mg.[26] These injections are clinically equivalent to human doses of approximately 28 and 70 mg/m$^2$, respectively.[119] Unfortunately, several local adjuvants were ineffective at blocking esorubicin ulcers in mice. These included cold, DMSO and glucocorticosteroids. Thus, esorubicin appears to be a more potent anthracycline than doxorubicin, both in antitumor activity and in toxicity. It is clearly a potent vesicant and may be less responsive to local adjuvants which are effective against doxorubicin extravasations.

### Cyanomorpholinyl Doxorubicin

Researchers at SRI International have synthesized extremely potent doxorubicin analogs with modifications at the nitrogen in the amino sugar moiety. The addition of a cyanomorpholinyl group at this position results in a compound with DNA alkylating activity and cytotoxic potency over 100-fold greater than doxorubicin.[120] In contrast, cardiotoxic effects are not similarly enhanced with cyanomorphilinyl doxorubicin. This imparts a greater therapeutic ratio to the analog.[121] However, experimental dermatotoxicity in mice is enhanced over 200-fold with the cyanomorpholinyl derivatives.[40] This is roughly comparable to the degree of enhancement in antitumor activity.[121] The cyanomorpholinyl doxorubicin compounds therefore comprise more potent vesicants which should be cautiously administered in clinical trials to avoid the potential for very severe extravasation necrosis.

### Liposomal Doxorubicin

Doxorubicin has been encapsulated into egg yolk phosphatidylcholine:cholesterol (55:45, mol:mol) unilamellar vesicles using a pH driven drug trapping mechanism. When injected subcutaneously into DBA/2J mice, these doxorubicin liposomes produced only minor local erythema and swelling and no ulcerations.[21] Equivalent doses of non-liposomal (free) doxorubicin produced significant ulcerations. Similar effects were noted with another liposomal formulation tested at 4-fold lower doxorubicin doses.[20] Thus, it appears that liposomal doxorubicin is markedly less ulcerogenic than doxorubicin when injected into skin tissues.

### Menogaril

(7-OMEN or Tomasar$^R$) is a semi-synthetic antitumor antibiotic related to the anthracycline doxorubicin (Adriamycin). In contrast to doxorubicin, menogaril has some oral activity and appears to concentrate in the cytoplasm rather than the cell nucleus.[40] Preclinical studies in mice were limited because the drug produced necrosis at the site of i.v. injection although the compound was negative in the eye and cheek pouch tests and in chronic dermal toxicity studies in rabbits.[40] However, when injected into pig skin, menogaril does produce dose-dependent skin ulcers and these lesions were partially blocked by the radical dimer, DHM3.[96]

In humans, menogaril predominantly causes phlebitis and there are a number of case reports of inadvertent perivenous extravasation without necrosis.[122] Typical reactions involve pain and swelling along the course of the vein used for infusion. This can occur in over half of the patients treated. While the local symptoms slowly resolve over a 1–2 week period, occasionally a palpable fibrotic 'cord' of venous scar tissue may remain. Long infusions (>2 h) and the use of highly concentrated drug solutions (≥ 1 mg/ml) may increase the severity of this reaction.[122] Thus, menogaril may best be de-

scribed as a local venous irritant in humans with a vesicant potential only if a large amount of highly concentrated solution were inadvertently extravasated.

## Other DNA Intercalating Agents

### *Mitoxantrone*

Mitoxantrone (Novantrone™) is an anthracene antitumor agent which intercalates into DNA and is active in acute leukemia and breast cancer. The usual dose-limiting toxicity of mitoxantrone is myelosuppression with decidedly less acute toxicities compared to other intercalators such as doxorubicin.[123] In like fashion, mitoxantrone does not appear to consistently produce necrosis if extravasated outside the vein. Table 3 shows that local tissue damage occurred in only 3 of 13 (23%) of patients experiencing a mitoxantrone extravasation. Interestingly, there was no mention of pain immediately after mitoxantrone extravasation. Surgery was performed in 2 of these patients to excise a $4 \times 6$ cm ulcer in 1 case[31] and to correct a flexion deformity in the elbow of another patient.[124] In the third patient, a 1.5 $cm^2$ mitoxantrone-induced ulcer spontaneously healed with only conservative local treatment.[28] Thus, most mitoxantrone extravasations produce only a blue discoloration of the skin and do not require extensive follow-up or local antidotal treatments.

The same pattern of a low vesicant potential for mitoxantrone has been noted in an experimental study in mice.[27] Intradermal mitoxantrone injections at clinical dose equivalents of up to 14 $mg/m^2$ did not produce skin ulceration in these animals. Instead, the animals experienced an intense blue discoloration of the skin with blanching and some short-lived induration over the site.[27] This contrasts greatly with the marked dose-dependent skin ulcers which are produced by intradermal doxorubicin injections in this same animal model.

### *Amsacrine*

This investigational acridine antitumor agent has been used in refractory acute myelogenous leukemia wherein the dose-limiting toxicity is myelosuppression. In preclinical studies, amsacrine produced local tissue irritation following subcutaneous or intramuscular injection.[125] This was thought to be due in part to the acidic drug vehicle. Another preclinical cutaneous toxicity study was prompted when dermal rashes were reported in workers who formulated the drug for clinical trials.[126] Amsacrine given for 14 days to guinea pigs and rabbits did not produce cutaneous lesions nor sensitization or systemic antibodies indicative of hypersensitivity.

When injected intradermally into dehaired mice, amsacrine produced dose-dependent skin ulcers at clinically equivalent dose levels.[26] Of interest, topical DMSO was the only local adjuvant which decreased these experimental amsacrine lesions. Cold, sodium bicarbonate and glucocorticosteroids did not reduce amsacrine lesions whereas topical heating significantly enhanced skin ulceration.[26]

In clinical studies, amsacrine diluted into 5% dextrose (to avoid precipitation in saline), produced phlebitis in the peripheral veins of 5–10% of patients.[127] One group reported an orange discoloration of the skin.[128] Pain and erythema at the injection site appear to be reduced when more dilute solutions and longer infusion times are used.[127] A single case of extravasation leading to skin necrosis has been reported for amsacrine.[129] In addition, the animal studies clearly indicate that amsacrine is a potential vesicant and can cause significant soft tissue toxicity if delivered outside the vein.[26,125,129] For these reasons, every attempt should be made to avoid extravasation of amsacrine and to use sufficient dilution in dextrose to reduce phlebitis. If extravasated, the studies in rodents suggest that topical DMSO may be beneficial.[26] This obviously requires verification in other models before a strong clinical recommendation can be made.

### *Dactinomycin*

This natural product is a potent DNA intercalating agent which contains two pentapeptide rings on a phenoxazine planar ring system. The drug is active in soft tissue sarcomas and trophoblastic cancer but is known to produce severe skin ulcers if extravasated.[15,16] In animal models, dactinomycin also pro-

**Table 3** Mitoxantrone extravasations in humans

| Intravenous dose ($mg/m^2$) | Incidence | Outcome Reference |
|---|---|---|
| 1.2–1.4 | 1/41 courses | No ulceration, some blue discoloration of skin, mild phlebitis in 10% of courses[28] |
| 4 (weekly) | 1/9 patients | Reversible blue skin discoloration |
| 12 | 1/86 patients | Phlebitis in 1 case resolved with hydrocortisone treatment. No ulceration upon extravasation in another case |
| 0.3–4 (daily × 5) | 3/25 patients | No ulceration[29] |
| 12 | Single case | Necrosis of a $4 \times 6$ cm dorsal hand area requiring excission 3 months after extravasation[31] |
| Not specified | 6/600 infusions | Elbow flexion deformity requiring surgery (1 case). 1.5 cm lesion healed spontaneously in another case. No local toxicity in 4/6 patients experiencing an extravasation[124] |

duces dose-dependant skin ulcers in mice,[17,26] guinea pigs[12] and marked local inflammation in rat paws.[14] However, the histologic pattern of dactinomycin skin damage in guinea pigs typically involves a 'bland coagulative necrosis' with acute inflammation noted only after low intradermal doses of the drug were administered.[12] There was no evidence of granulation tissue in any of the dactinomycin-treated guinea pigs.[12] Dactinomycin antidote studies in mice have shown that neither topical cooling[24] nor topical DMSO are effective local treatments.[26] While the efficacy of cooling was not consistent between the two mouse studies, other in vitro trials have demonstrated reduced cellular accumulation of dactinomycin at low temperatures. On the other hand, corticosteroids like hydrocortisone were not markedly effective in either mouse study.[17,26] Other ineffective dactinomycin 'antidotes' include heat, saline, sodium thiosulfate, hyaluronidase and beta-adrenergic agents.[17,26] The application of heat in one mouse study significantly increased dactinomycin skin ulcers.[26]

## DNA Alkylating Agents

### *Mechlorethamine*

Mechlorethamine or nitrogen mustard ($HN_2$), is the prototype bifunctional alkylating agent which is highly active in Hodgkin's disease and other lymphomas. Its activity as a vesicant is well based since it was a direct descendant from the sulfur mustard 'blister' gasses used with devastating toxic effects in World War I. While $HN_2$ has been used as a topical solution to treat mycosis fungoides, the extravasation of the drug during intravenous administration is known to produce severe and prolonged skin ulcers.[18] In one series, $HN_2$ extravasations on the dorsum of the hand required 4–5 months to heal and even skin grafting was ineffective in 1 patient.[18] Mechlorethamine extravasations produce immediate pain and swelling and thrombophlebitis of the vein is common.[19] Reportedly this can be lessened by administering the $HN_2$ as a side port injection into the tubing of a freely flowing i.v.[19] Thus, $HN_2$ is highly toxic to veins even when no extravasation occurs. In 1 patient, a severe perivenous hyperpigmentation occurred which required over 4 months to clear. Interestingly, this reaction, which was painless, spread slowly up the hand and arm and ultimately involved the anterior thorax.[49]

### *Mechlorethamine Systemic Antidote Studies*

Sodium thiosulfate ($Na_2S_2O_3$) has been comprehensively evaluated as an antidote to nitrogen mustard. Hatiboglu et al found that intravenous sodium thiosulfate could neutralize $HN_2$ in mice and dogs. It was maximally effective when thiosulfate preceded $HN_2$ administration by 15 min and had no protective effect when given 5 min after $HN_2$.[130] The effective dose ratio in this study was 120:1 (thiosulfate: $HN_2$ on a mg/mg basis). Additionally, intravenous thiosulfate did not protect mice from ulcerations produced by a subcutaneous $HN_2$ injection.[130] This demonstrates that systemic (i.v.) sodium thiosulfate is ineffective as a local antidote to $HN_2$-induced skin ulceration.

In contrast, intravenous sodium thiosulfate was an excellent bone marrow protectant for $HN_2$ given into the carotid artery,[131] but it did not antagonize systemic, emetogenic or local neurologic effects from the drug. These latter effects included supraorbital skin discoloration, periorbital edema, hair loss and neurologic toxicity. Thus, it is clear that thiosulfate given systematically, cannot block local $HN_2$ effects, and that any antidotal effects are due to direct chemical complexation of $HN_2$ with thiosulfate.[132]

### *Mechlorethamine Clinical Extravasations*

Sodium thiosulfate is recommended for use as a local antidote to accidental $HN_2$ extravasation by the manufacturer or Mustargen.[133] A 1/6 M (isotonic) sodium thiosulfate solution is described for this emergency use. In one anecdotal report, the 1/6 M solution was used to treat an inadvertent intramuscular injection of 30 mg $HN_2$ into the buttock of a 55-year-old psoriasis patient. While the thiosulfate regimen was delayed by 5 h, this regimen (5 ml of 1/6 M solution given intramuscularly for 5 doses), completely prevented subsequent skin ulceration.[134] Interestingly, the peripheral white blood count remained stable in this patient suggesting a systemic antidotal effect for thiosulfate.

### *Mechlorethamine Local Antidote Studies*

In an experimental study using dehaired BALB/c mice, $HN_2$ was shown to produce dose-dependent skin ulcers after intradermal injection of doses equivalent to 1.4–7 mg/m$^2$ in humans.[135] A variety of local adjuvants were evaluated to block skin ulceration. These included sodium chloride dilution, hyaluronidase, sodium thiosulfate, dimethylsulfoxide, hydrocortisone, heat and topical cooling. Dimethylsulfoxide, and hyaluronidase both increased $HN_2$ skin ulcers. Thiosulfate was the only effective regimen against $HN_2$ ulcers. A high concentration of 0.34 M thiosulfate given immediately after $HN_2$ was most active. Delayed thiosulfate injections, or the use of less than a 200:1 dose ratio (thiosulfate:$HN_2$) were not effective.

These results corroborate the single clinical case[134] and the manufacturers recommendations.[133] Clearly, sodium thiosulfate is well tolerated and highly effective as a local (subcutaneous) treatment of $HN_2$ extravasation. The role of topical cooling does not appear to be substantiated as an $HN_2$ antidote.

## Mitomycin C

Mitomycin C is an antibiotic with significant antitumor activity in a variety of solid tumors, particularly adenocarcinomas of the breast and gastrointestinal tract.[136] At least two mechanisms of action are postulated for this drug; bifunctional alkylation producing DNA crosslinks [137] and the production of oxygen free-radicals via redox cycling of the quinone group.[138] In addition to dose-limiting myelosuppression, mitomycin C can produce severe soft tissue necrosis upon inadvertent extravasation.[20–22] Characteristically, these lesions progress slowly over weeks to form open ulcers which can involve deep anatomic structures. Surgical excision is often needed to prevent damage to nerves and tendons.

### *Mitomycin C Clinical Extravasations*

In a series of 3 patients experiencing mitomycin C extravasation, severe pain and swelling were noted during an intravenous infusions through superficial veins on the hand, wrist and forearm.[21] Despite corticosteroid treatment in 1 case (300 mg hydrocortisone injected, and 0.1% triamcinolone cream applied topically), all 3 extravasations progressed to painful ulcers within 2 weeks of the event. Subsequently, all 3 patients were treated with surgical debridement which provided good local pain control. Two patients then went on to have successful split thickness skin grafting.

In one of the cases previously described, delayed skin ulcers appeared at a prior mitomycin C infusion site following a second treatment given into the opposite arm. This 'recall' type of extravasation response occurred 75 days after the first mitomycin C injection and is reminiscent of delayed radiation recall phenomena seen with combinations of anthracyclines and ionizing radiation.[139]

In other clinical series, a similar delayed pattern of mitomycin C necrosis has been noted.[20,140,141] In 8 patients the mean time lapse from mitomycin administration to apparent skin injury was over 3 months (range 1–29 weeks).[20] Five of these 8 patients developed skin ulcers requiring surgery and there was no evidence that local corticosteroids were helpful at preventing or reducing ulcers. Most distressing though was the fact that none of these 8 patients complained of pain or irritation during or immediately after the mitomycin C infusion. Furthermore, some ulcers occurred at sites of prior mitomycin C administrations (mitomycin recall injury). In 2 other cases, mitomycin C ulcers occurred at the site of blood withdrawal from the patient's wrist. These lesions appeared 1–3 h after drug administration at the ipsalateral mid-forearm area.[22]

One clinician has suggested that supravenous generalized hyperpigmentation after an initial mitomycin C infusion may herald second-dose ulcerations which can occur at both the prior and current administration sites.[142] In both of these cases, surgical debridement and skin grafts were required to close multiple, coalescing mitomycin C skin ulcers. In another case, sunlight appeared to markedly exacerbate an indolent mitomycin C extravasation on the forearm.[143] Alcoholic beverages were similarly postulated to acutely precipitate a mitomycin C ulcer in an otherwise asymptomatic Japanese patient.[130] This reaction occurred 3 months after the patient experienced a 'painless' mitomycin C extravasation into the dorsum of the hand. In another case, an ulcer developed on the dorsum of a patient's finger which had been inadvertently pricked with a needle containing mitomycin.[144]

These cases notwithstanding, most mitomycin C extravasations produce immediate local symptoms of pain and swelling.[21] Glucocorticosteroids appear to offer no benefit as a means of treating immediate or delayed mitomycin C extravasation injuries. This is also reinforced by the negative experimental mitomycin C skin toxicity studies with hydrocortisone used in rabbits[78] and in mice.[145]

### *Mitomycin C Experimental Antidote Studies*

In the intradermal mouse model, a number of potential local antidotes to mitomycin C ulceration have been tested. Table 4 summarizes the lack of efficacy for most of the pharmacologic agents as well as heating and cooling.[145] Only two compounds were found to have antidotal activity against mitomycin C skin ulcers in the mouse. These were topical DMSO (99%), and intradermal sodium thiosulfate (0.34 M). While topical DMSO was highly effective when applied immediately after mitomycin C, it was inactive in mice treated 1 h after mitomycin C was injected into the skin. This suggests that DMSO might be useful for clinical mitomycin C extravasations if immediate symptoms are produced. Delayed and/or distal mitomycin C extravasation reactions may not be as amenable to topical DMSO treatment. And, in one clinical anecdote, a single DMSO application was ineffective at blocking mitomycin C extravasation necrosis.[146] This suggests that a more aggressive topical DMSO schedule, such as is recommended for doxorubicin,[105] may be necessary for treating mitomycin C extravasation. The role of the sulfur nucleophile sodium thiosulfate in managing mitomycin C

**Table 4** Potential mitomycin antidotes evaluated experimentally

| *Ineffective* | *Effective experimentally* |
|---|---|
| Hyaluronidase[145] | Dimethyl sulfoxide[145] |
| Heparin[145] | |
| Diphenhydramine[145] | |
| Isoproferenol[145] | Sodium thiosulfate[145] |
| Hydrocortisone[21,78,145] | |
| Fumaric acid | Radical dimer (DHM3)[96] |
| Vitamin E[145] | |
| Lidocaine[145] | |
| N-acetylcysteine[145] | |

extravasations is not established. While thiosulfate is highly efficacious as an antidote against other alkylating agents, such as mechlorethamine, its efficacy against mitomycin extravasations is unclear.

In pigs given mitomycin C, antidotal activity has been described for the radical dimer DHM3.[96] While not as effective as with the anthracyclines, DHM3 was able to roughly halve mitomycin C skin lesions using a high molar ratio of >20:1 (DHM3:mitomycin C). This again argues for further development of radical dimer compounds for use as local antagonists to extravasations of quinone-containing anticancer agents.

Clearly, topical DMSO needs to be evaluated in the clinic as an antidote to mitomycin C extravasations. The difficulties in controlling this type of study are manifestly increased by the occasional asymptomatic, delayed, and/or distal presentation of mitomycin C skin lesions. Nonetheless, the consistent reports of activity for DMSO in the mitomycin C animal studies does suggest it may have a role in modulating mitomycin C skin ulcers in humans.

Ludwig et al have reported 1 patient treated with topical DMSO for a 0.32 mg mitomycin C extravasation on the forearm.[89] A solution of 90% DMSO and 10% vitamin E were applied as dressings to the site, every 12 h for 2 days. No ulceration was apparent in this single case.[89]

## Other DNA Binding Agents

### *Carmustine*

Carmustine or bis-chloroethyl nitrosourea (BCNU) is a highly lipophilic antitumor agent which produces DNA crosslinking and protein-carbamoylating methylisocyanate metabolites in tumor cells.[147] It is active in lymphomas and in brain cancer wherein it is typically given as a brief infusion. Phlebitis is routinely encountered with BCNU infusions[148] but there are no reports of extravasation leading to necrosis.

In a BCNU toxicity study in mice, the drug produced only mild induration even when highly concentrated injections of lethal doses were given intradermally (Dorr, unpublished observations). Thus, after I.D. doses of up to 2 mg/mouse (equivalent to 290 mg/m$^2$ in humans), only mild, short-lived induration occurred on the backs of dehaired BALB/c mice. These injections proved lethal to the mice after a few days. Lower, non-lethal I.D. BCNU doses proved similarly inactive as skin vesicants.

Carmustine therefore does not appear to be a vesicant and extravasations of this agent should be managed conservatively without local injections or topical application of pharmacologic agents. However, if topically spilled or splashed on the skin, it may be possible to inactivate carmustine with an 8.4% sodium bicarbonate solution in which the drug is chemically degraded.[149] The phlebitis produced by carmustine infusions probably relates more to the ethanol used for drug reconstitution, rather than an effect of the nitrosourea. Therefore, adequate dilution of carmustine solutions into at least 250 ml of 5% dextrose or saline may dramatically lessen this otherwise frequent toxicity.

### *Cisplatin*

Cisplatin is believed to produce antitumor effects by binding to DNA in a process somewhat similar to the classical alkylating agents.[150] Reports of severe local toxicities with this agent are rare, although this drug, like other heavy metals, can rarely cause topical allergic hypersensitivity reactions.[151] The paucity of injection site problems with cisplatin may relate to its routine dilution in large volume parenteral saline solutions. This practice dramatically lessens cisplatin infusion concentrations and thereby diminishes the likelihood that a large ulcerogenic cisplatin dose could be extravasated in typical clinical settings.

A few case reports describing cisplatin extravasation injuries are available. Importantly, each has unusual features which differentiate it from the typical clinical use of the drug. In the first case, mild fibrosis and moderate cellulitis developed on the forearm of a patient treated with a concentrated, 0.42 mg/ml, cisplatin solution.[44] This lesion was initially treated with warm soaks and peaked in intensity after 2 weeks. It then slowly resolved over the next 2 months. No skin ulcers or limitation of motion were noted and cisplatin was readministered twice to the patient without incident. In the second case, a highly concentrated cisplatin infusate (0.75 mg/ml) extravasated into the dorsum of the hand of a confused 67-year-old patient.[43] It was felt that much of the 100 ml infusate had extravasated, possibly due to the patient's continued attempts to remove i.v. lines. No local pharmacologic treatment was used and over the next 2 weeks pain, swelling and inflammation ensued. A large necrotic lesion then developed, involving extensor tendons and subcutaneous fat. This was eventually treated with surgical debridement and split thickness skin grafts.

In the final case, a cisplatin arterial infusion (1 mg/ml) extravasated from the right humeral artery in a 48-year-old fibrosarcoma patient. While only 1.5 ml was felt to have extravasated, local corticosteroids were injected into multiple subcutaneous sites around the extravasation area. Despite this, erythema and edema led to a vesicular eruption after 6 days. Topical corticosteroids and antibiotics were then prescribed. One month later a 3 cm black scar was apparent on the forearm. No details on the resolution of this lesion were provided.[43]

These 3 cases are similar in that highly concentrated cisplatin solutions (>0.4 mg/ml) were infused in unusual clinical circumstances. Frank ulceration occurred in 2 patients and local corticosteroids were not helpful in 1 of these patients. In contrast, there is

a large body of clinical data which suggests that extravasations of more dilute cisplatin solutions do not produce serious local toxicity. In one experimental skin toxicity study in mice, cisplatin did not produce ulcers even when lethal doses were injected intradermally.[27]

Therefore, in most clinical settings, cisplatin does not appear to be an extravasation vesicant and no local therapy, pharmacologic or otherwise is indicated. If however, a large amount of a concentrated solution is inadvertently extravasated, local ulceration is possible and should be treated immediately with sodium thiosulfate which is known to inactivate cisplatin on contact.[152] The same isotonic, 0.16 M thiosulfate solution recommended for mechlorethamine, should be used for treating concentrated cisplatin extravasations. The dosing of sodium thiosulfate as a local cisplatin antidote is unexplored. In this setting, it might be reasonable to use the thiosulfate regimen recommended for mechlorethamine: 2 ml of 10% sodium thiosulfate for each mg of cisplatin extravasated.

*Dacarbazine (DTIC)*

DTIC is a triazene-containing anticancer agent which although similar in structure to an inosine-based ribonucleotide, appears to act principally as a DNA alkylating agent in tumor cells.[153] Two possible activation pathways for DTIC are described; light-induced conversion to 5–diazo–imidazole–4–carboxamide, and microsomal oxidation leading to the release of a methyl-diazonium ion which can alkylate DNA. The light-induced activation pathway is reportedly responsible for the occasionally severe phlebitis produced by infusions of drug solutions from clear containers.[154] Phlebitis, however, is rare and no reports of extravasation necrosis were uncovered. However, in patients given high dose DTIC therapy, a severe facial hypersensitivity to sunlight is described.[155]

Studies in mice have shown that only very large intradermal DTIC doses produced skin ulcers (equivalent to $>250$ mg/m$^2$ doses in humans).[46] Thus, like cisplatin, it is highly unlikely that a sufficient DTIC dose could be extravasated from typical infusion solutions to produce local skin ulcers. Therefore, in typical clinical settings, small DTIC extravasations should not produce necrosis. However, the drug does have this potential if a highly concentrated DTIC solution inadvertently leaked from the vein during intravenous injection.

In the mouse model, even large DTIC doses of 10 mg, equivalent to 1420 mg/m$^2$ in humans, produced small ulcers which healed briskly within 20 days. Of interest, these skin lesions were much more severe if mice were exposed to strong light after injection but not when DTIC solutions were light-exposed prior to injection. A variety of potential local adjuvants were tested to reduce DTIC skin lesions. In this model, inactive adjuvants included heat, cooling, topical DMSO, hyaluronidase, saline and hydrocortisone. Two procedures reduced DTIC lesions in the mouse model; pre-exposure of drug to an S–9 microsomal enzyme mixture, and a local (intradermal) injection of hypertonic (0.33 M) sodium thiosulfate.[46] In summary most extravasations of DTIC solutions should not produce necrosis and should be managed conservatively with attention to protect exposed tissues from light following drug administration.

**Vinca Alkaloid Extravasations**

The vinca alkaloids vincristine (Oncovin) and vinblastine (Velban, others) are known to be vesicants which produce pain and necrosis following inadvertent extravasation.[50,52,53] Unfortunately, many of these extravasations occur in children receiving vincristine for solid tumors[156] or leukemias.[145,146] Typically, vincristine extravasations produce marked pain, erythema and localized swelling within minutes. Skin blisters form after several days and then resolve slowly over several weeks. Fortunately, most vinca alkaloid extravasations do not produce frank skin ulceration.[57]

In one case report, skin ulceration occurred on the dorsum of the hand several weeks after an asymptomatic 8 h infusion of vinblastine in a peripheral vein.[52] Interestingly, this patient had a prior history of parenteral drug abuse and had received an arteriovenous fistula on the same arm used for the vinblastine infusion. It was believed that incomplete venous obstruction of the fistula produced the extravasation by causing a retrograde flow of blood in the distal vein used for the infusion.[52] The painful skin necrosis in this patient resolved slowly over 6 months without the need for local surgery.

*Delayed Vinca Extravasation Symptoms*

In another report, an unusual delayed presentation of extravasation symptoms was described in cancer patients receiving the investigational vinblastine derivative, vindesine by peripheral vein injections.[53] Extravasation symptoms of pain and swelling at the injection site did not occur immediately in these patients, but instead was delayed for periods of several hours up to 1 day after drug administration. These vindesine extravasations occurred from veins on the dorsum of the hand and produced severe, painful skin ulcers after 3 weeks which healed slowly over a 6-month time period. Oftentimes, delayed extravasation symptoms included local tingling paresthesias with some residual sensory deficits even after the skin lesions had superficially healed.[53]

The vinca alkaloids have also been given by prolonged intravenous infusions to enhance cell cycle (phase)-specific tumor cell killing. Painful extravasations from peripheral veins have been described in such regimens involving both vincristine[157,158] and

vinblastine.[159] Skin necrosis was not described in these reports but there was a high frequency of local swelling and phlebitis in 3 of 30 vincristine infusion patients and in 3 of 12 vinblastine infusion patients. While these local reactions resolved after 1–2 weeks without therapy, the severity of this complication clearly mandates that peripheral veins *not* be used for protracted vinca alkaloid infusions.

### *Vinca Clinical Antidote Reports*

A wide variety of putative antidotes to vinca alkaloids have been suggested. These include folinic acid,[160] glutamic acid,[161] sodium bicarbonate,[78] hyaluronidase[162] and glucocorticosteroids.[163,164] As with most purported extravasation antidotes, no well controlled clinical studies are available to support efficacy claims. Again, this is largely due to the unpredictable nature of clinical extravasations as well as the varying and usually unknown amounts of drug extravasated in each instance. In 2 brief case reports, subcutaneous hydrocortisone, 100 mg, was used to treat extravasations of vincristine sulfate.[163,164] Pain and swelling were present in all 3 patients but no skin necrosis occurred.

The absence of frank necrosis however, is quite compatible with the outcome of untreated or conservatively (non-pharmacologically) managed vinca alkaloid extravasations described earlier.[57] For example, Larson has described a patient experiencing an extravasation of a vincristine infusion (.02 mg/ml in 5% dextrose solution) wherein the use of 50 mg prednisolone and local cooling did not prevent subsequent pain and swelling which ultimately required surgical excission and skin grafting.[57] However, as discussed below, both cooling and corticosteroids have been shown to significantly enhance vinca alkaloid skin lesions in experimental animal models.[23] Thus, the lack of objective endpoints and essential controls severely constrains conclusions of antidote efficacy from anecdotal clinical reports.

### *Vinca Experimental Antidote Studies*

Vinca alkaloid skin toxicity has been studied in a number of rodent models. In guinea pigs, subcutaneous vincristine and vinblastine were non-toxic.[73] This is similar to studies with subcutaneous doxorubicin.[69] In contrast, intradermally injected vinca alkaloids produced severe ulceration at all doses tested, including a dose equivalent to 1% of human vinca therapeutic doses adjusted on a body surface area basis.[73] Skin toxicity did not result from prior sensitization but instead occurred as a direct, immediate consequence of drug injection into the skin.[73] Histologically, vinca skin lesions in the guinea pig were associated with acute hemorrhagic inflammation and preservation of granulation noted by capillary and fibroblast proliferation.

In contrast, Buchanon et al produced vincristine skin lesions in mice only after a repeated intradermal administration involving a seven day interval.[17] The pattern of diffuse punctate lesions following vincristine also suggested a local hypersensitivity etiology. In rabbits, intradermal vincristine injections similarly produced inconsistent skin ulcers which developed slowly over 7 days and resolved 17 days after injection.[165] Histopathology of these lesions showed neutrophilic infiltration and dermal separation within days of injection. Despite this pattern of inflammatory response, local intradermal injections of dexamethasone, 0.8 mg, did not significantly reduce or prevent either the variable presentation skin ulceration nor the more consistent occurrence of induration following vincristine.[165]

**Table 5** Experimental antidote studies for skin toxicity from vinca alkaloids in the mouse[23]

| *Ineffective vinca antidotes* | Effective vinca antidotes |
|---|---|
| Calcium leucovorin (folinic acid) | Normal saline |
| Diphenhydramine | Hyaluronidase |
| Hydrocortisone* | Topical heating |
| Isoproterenol | |
| Sodium bicarbonate | |
| Topical cooling* | |
| Vitamin A cream* | |

* Significantly *increased* vinca skin ulcers in the mouse

In an antidotal survey of mice given intradermal vinblastine or vincristine, only two procedures consistently reduced vinca alkaloid skin ulcers.[23] These were intradermal injection of hyaluronidase (5–15 units), and mild topical warming of the skin (Table 5). Other putative antidotes which were inactive in the mouse model included folinic acid and sodium bicarbonate. In contrast, local skin cooling and hydrocortisone injection significantly increased vinca alkaloid skin ulcers.

### *Hyaluronidase: An Effective Local Antidote*

Studies with radiolabeled vinblastine clearly documented the ability of heat and especially hyaluronidase, to rapidly disperse vinblastine from skin tissues. Thus both hyaluronidase and heat act to enhance the systemic uptake of vinca alkaloids from skin tissues.[23] Hyaluronidase is well known to act as an enzymatic 'spreading factor'.[166] It chemically acts to temporarily dissolve hyaluronic acid bonds which hold tissue planes together.[167,168] Hyaluronidase has long been advocated as an adjuvant to increase subcutaneous fluid absorption and to aid in drug resorption from subcutaneous spaces.[169] The typical dose recommendation in this setting has been 150 turbidity reducing units of enzymatic activity. Of interest, hyaluronidase has also been shown to be useful in preventing soft tissue necrosis from extravasations of antibiotics such as nafcillin in neonates (15 units injected into site)[168] and in experimental extravasations of hyperosmolar parenteral nutrition solutions[169] or radiopaque con-

trast media.[170] The lack of significant local or systemic toxicity with hyaluronidase also argues strongly for its routine use as a vinca alkaloid extravasation antidote.

Hyaluronidase cannot be used with anthracycline extravasations since it significantly *increases* experimental skin ulceration. It is similarly contraindicated for injection into infected or cancerous tissues since dissemination of these diseases would be facilitated. Hyaluronidase also reduces experimental skin lesions from massive doses of epipodophyllotoxins such as etoposide (VP-16) [see below].[44] It is of no benefit in treating experimental skin toxicity produced by the alkylating agents mitomycin C[145] and mechlorethamine.[135]

*Epipodophyllotoxins*

The semisynthetic epipodophyllotoxins etoposide (VP-16) and teniposide (VM-26) have each been associated with phlebitis and local swelling at the injection site.[171] And, there is at least one description of severe skin ulceration following the extravasation of etoposide in humans.[8] The relative lack of reported cases may relate to the use of dilute infusion solutions for these drugs. This practice limits the total amount of drug which could be delivered outside of the vein during an extravasation. In addition, the phlebitis from the agents may relate to the use of irritating emulsifying agents such as polysorbate 80 and Cremophor™ in the clinical formulations of etoposide and teniposide, respectively. Thus, it is well known that lipophilic detergents like Cremophor and polysorbate 80, can produce local skin toxicity when given subcutaneously in animal models.[172]

Accordingly, an experimental epipodophyllotoxin skin toxicity study in mice has demonstrated the ulcerative potential of the commercial etoposide cosolvent system alone.[51] The major toxic component was the polyethoxylated castor oil component in the Cremophor™ solvent system which produced dose-dependent skin ulcers in mice. Although animals given highly concentrated intradermal solutions of etoposide or teniposide did form small skin ulcers, these were produced only when the equivalent of a systemically toxic dose was injected intradermally in a small volume of diluent. This means that skin ulcerations from clinical epipodophyllotoxin extravasations are highly unlikely because typical drug dilutions in the clinic are quite large. Notwithstanding this conclusion, the mouse skin toxicity studies were able to document epipodophyllotoxin diluent-induced skin ulcers in mice.[51] In addition, antidote studies in the mouse demonstrated reduction and prevention of epipodophyllotoxin ulcers using intradermal hyaluronidase injections.[51] This is similar to the findings with the vinca alkaloids. Thus, if presented with a large extravasation of a highly concentrated epipodophyllotoxin solution in the clinic, a subcutaneous hyaluronidase injection (150 units in 3 ml of 0.9% sodium chloride) would be useful to prevent both local pain and swelling as well as potential, but unlikely skin ulceration.

**Extravasation Management Guidelines**

Surgery to remove non-viable tissue and entrapped drug, is unequivocally the best method available to mitigate the damage from large evolving skin ulcers. However, since as few as a third of all vesicant extravasations will ulcerate,[57] the routine use of surgical excision is obviously not warranted. Larson's guidelines suggest that severe pain at an extravasation site 7–10 days after the event, may adequately select those patients needing surgical management.[57] In addition to pain, new procedures are described for detecting locally entrapped drug using either simple fluorescence[173] or high performance liquid chromatography.[63]

*Detecting Drug in Tissues*

The extent of surgery should be sufficient to leave wide margins of viable skin free of locally entrapped drug. If inadequate, repeated surgical procedures have been required to obtain adequate margins to facilitate secondary closure of the wound.[63] Again, fluorescence or HPLC studies may be a guide to determining the extent of drug spread, at least for the anthracyclines. Unfortunately, for most other vesicants including the alkylating agents and the vinca alkaloids, no specific assays are available to guide the surgeon. Intraoperative fluorescein injections are also recommended as a means of demarcating viable tissues.[74,91] In one report, fluorescein injections were combined with drug fluorescence to simultaneously detect viable cells and deposits of anthracyclines such as doxorubicin.[175]

It is not the intent of this review to cover standard surgical practices for treating extravasation injuries and several references are already cited.[57–60,69,70] However, it is abundantly clear that early surgical referral for large, painful lesions, may dramatically help to mitigate subsequent tissue damage, and can help to spare the involvement of important subcutaneous neural, vascular and motor structures.[1,2] This latter point is particularly relevant to vesicant extravasations on the dorsum of the hand.[175]

*Other Non-pharmacologic Procedures*

The immediate removal of any extravasated fluid using the original indwelling needle or catheter is highly indicated in managing any vesicant extravasation.[8,39] While evacuation is usually not possible due to blockage at the needle tip, it can occasionally be rewarded with the recovery of substantial amounts of drug.[8,39] The original needle or catheter can also be left in place to aid in the delivery of a local antidote thereby obviating the need for additional injections. The experimental study of Upton et al should also be kept in mind since multiple, or 'pincushion' injections

**Table 6** Recommended chemotherapy extravasation antidotes

| Chemotherapy class, vesicant agent(s) | Recommended antidotal maneuvers | Specific regimens |
|---|---|---|
| *Alkylating agents* | | |
| Mechlorethamine | 0.17 Molar sodium thiosulfate | Mix 4 ml of 10% sodium thiosulfate USP with 6 ml sterile water for injection |
| Cisplatin* | | 2 ml into site for each mg of drug extravasated |
| Mitomycin C | 50% (v/v) Dimethyl-sulfoxide (Sol Rimso-50®, Research Products, Inc) | Apply 1.5 ml topically to site every 6 h for 7–14 days. Allow to air dry |
| *DNA intercalating agents* | | |
| Doxorubicin, Daunomycin Others | Cold application | Apply immediately without pressure, rotate on and off for 24 h |
| | 50% (v/v) DMSO solution (optional) | Apply 1.5 ml topically on site every 6 h for 14 days; Allow to air dry |
| *Plant alkaloids* | | |
| Vinblastine, vincristine | 150 units hyaluronidase (Wydase®, Wyeth Laboratories) | Reconstitute 150 u in 1–3 ml of saline, inject into site using original needle if possible |
| | Warm pack | Apply to site without pressure after hyaluronidase |
| Epiodophyllotoxins* (VM-26, VP-16) | 150 u hyaluronidase | Use same schedule as for vincas |

* Treatment not typically recommended since the drugs are not ulcer-causing unless a large amount of a higly concentrated solution is extravasated

of hydrocortisone in the rat model actually increased doxorubicin ulceration areas.[75] The use of the original needle is especially relevant to mechlorethamine and vinca alkaloid extravasations wherein highly effective antidotes are well known and require close regional delivery if not direct contact with the extravasated drug for maximum efficacy.

The use of pressure on chemotherapy extravasations is always contraindicated. Even slight pressure on an extravasated area could spread the vesicant agent over a much broader area. Likewise, elevation of an effected area is highly recommended since this may aid in the normal absorption and drainage of loculated extravasated fluids.

The role of heating and cooling has been reviewed with the individual agents. In summary, mild local heating is quite effective for vinca alkaloids[23] but detrimental, indeed synergistic, with anthracyclines especially doxorubicin.[108,109] For the alkylating agents mechlorethamine[135] and mitomycin C[145] neither heating nor cooling were effective experimentally.

## Summary

### *Pharmacologic Extravasation Antidotes*

The foregoing sections have reviewed the experimental studies and clinical anecdotes describing potential pharmacologic antidotes to extravasations of vesicant anticancer agents. Numerous prior reviews have also suggested specific antidotes[64,176–179] or very conservative, non-pharmacologic approaches.[57,180] Many antidotal approaches to extravasation have not been experimentally validated and thus, few 'antidotes' share a rationale which is founded on positive experimental and clinical studies. However, using this criteria, a few active antidotes can be distilled from the literature. These are outlined in Table 6. These antidotes include isotonic (1/6 M) sodium thiosulfate for mechlorethamine (and optionally for cisplatin), hyaluronidase for the vinca alkaloids (and optionally for epipodophyllotoxins such as etoposide), and cooling with very topical DMSO and low dose hydrocortisone for the anthracyclines.[181] For the alkylating agent mitomycin C, topical DMSO has been effective experimentally but has not yet received clinical validation, at least in published studies. Nonetheless, the severity of mitomycin C ulcerations[21] and the documented safety of topical DMSO in the small series of doxorubicin extravasation patients[105] argues for its use when mitomycin extravasates in the clinic. Furthermore, except for DMSO, all of these extravasation antidotes are listed in the official FDA-approved package inserts for each vesicant agent. Thus, the inserts for vincristine and vinblastine specify hyaluronidase, for doxorubicin, glucocorticosteroids, and for mechlorethamine, sodium thiosulfate.

New studies are clearly needed to clarify the role of topical DMSO with anthracyclines and mitomycin C. In addition, efforts should be made to begin clinical development of radical dimers such as DHM3 which can directly inactivate quinone-containing vesicants like doxorubicin and mitomycin C.[96] Although the incidence of chemotherapy extravasation may be lessened with vascular access devices, it nonetheless, continues to comprise a serious and highly litigious area of oncology practice. This commands continued extravasation intervention studies and diligent prevention when ever possible.

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