



Review Article

Chemotherapy-Induced Extravasation Injury: Classification and Management

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Abstract

Chemotherapy is a category of medicines that is utilized to kill and eradicate immediately the abnormally growing cells in the body. It is commonly utilized to treat cancer because cancer cells grow and divide at a faster rate than other cells. Extravasation is the mechanism by which any liquid (fluid or drug) accidentally enters the surrounding tissue. Extravasation in cancer treatment indicates the unintentional chemotherapy infiltration into the subdermal tissues or subcutaneous enclosing the intravenous or intra-arterial location of administration. Extravasated agents are categorized as vesicants, exfoliants, irritants, inflammators, and neutrals. Based on their potential for causing harm, management of chemotherapy-related extravasation includes both non-pharmacological treatment and pharmacological treatment.

Keywords: Adverse effect, cancer chemotherapy, extravasation, toxicity.

اضرار فرط التسريب خارج الأوعية للعلاج الكيميائي: التصنيف والعلاج

الخلاصة

العلاج الكيميائي هو فئة من الأدوية الكيميائية التي تستخدم للقضاء على الخلايا السرطانية سريعة النمو في الجسم. يستخدم عادة لعلاج السرطان لأن الخلايا السرطانية تنمو وتنقسم بمعدل أسرع من الخلايا الأخرى. فرط التسريب خارج الأوعية الدموية هو الآلية التي يدخل بها أي سائل (سائل أو دواء) عن طريق الخطأ إلى الأنسجة المحيطة. ويشير فرط التسريب في علاج السرطان إلى تسيل العلاج الكيميائي غير المقصود إلى الأنسجة تحت الجلد أو تحت الجلد الذي يحيط بموقع الإعطاء عن طريق الوريد أو داخل الشرايين. يتم تصنيف العوامل التي تسبب الضرر نتيجة لفرط التسريب خارج الأوعية على أنها مسبب التقرحات، مقشرات، مهيجات، مسبب الالتهابات، والعوامل المحايدة. بناء على قدرتها على التسبب في الضرر، تشمل طرق علاج مثل هذا الضرر المرتبط بالعلاج الكيميائي كلا من العلاج غير الدوائي والعلاج الدوائي.

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INTRODUCTION

Cancer is the most well-known cause of death worldwide and the second-leading cause of death in the United States. Given the conventional rise in cancer proportion and prevalence, a medicine physician is likely to encounter patients on chemotherapeutic

agents. The field of chemotherapeutic agents is broad, and adverse effects are disastrously common. By reason of the disease's complexity, the superiority of patients is given multidrug regimens [1]. Distinguishing disease pathology from adverse chemotherapeutic effects remains difficult. To manage severe toxicity, it is often necessary to

discontinue exposure. Afterward, since the presentation of systemic chemotherapy as a therapy for both solid and hematological malignancies over the last 50 years, its use has steadily increased. Intravenous infusion is the primary mode of anti-cancer drug administration for the majority of malignant derangements, with over 1 million infusions performed every day worldwide [2]. Both patients and the medical team are concerned about the safety of chemotherapy administration. Chemotherapy extravasation is defined as the unexpected infiltration of chemotherapy into the subdermal or subcutaneous tissue at the site of injection [2-6], which can result in tissue necrosis. Because of the general lack of reporting and the lack of a centralized registry of chemotherapy extravasation events, the exact incidence of chemotherapy extravasation varies greatly. When chemotherapy is administered recklessly or unintentionally into the perivascular area or subcutaneous tissue rather than the vessels, iatrogenic injury results, which is known as extravasation of an anticancer drug. Genuinely, intravenously administered agents are categorized into five groups based on their capability to harm: vesicants, exfoliants, irritants, inflammitants, and neutrals [7]. Extravasation causes subcutaneous tissue, skin, peripheral ligaments, the vascular system, the thorax, and tendons to experience injuries ranging from local irritation to complete necrosis. This criterion, in its most severe form, can cause constant functional impairments, significantly lowering patients' quality of life. Vesicant injuries can occur in hours or days and may threaten the extension of chemotherapy; as a result, these side effects are classified as serious oncologic necessity [8]. Regardless of avoidance measures (secure administration, the presence of local policies and protocols, and the training of appropriate staff members), the proportion range of extravasation varies between 0.01 and 7.0%, depending on the studies. extravasation is still common when administered via a central venous access device, with rates ranging from 0.26% to 4.7% [9,10]. This adverse effect of cytotoxic agent extravasation may be

exacerbated by the variety of treatments with chemotherapy that patients can accept over a course of years [11]. Nonetheless, there is a demand to be capable of providing the maximal quality and competence of responsibility while regulating the brunt of treatments on patient results. However, chemotherapy extravasation management debris is questionable, and there is no categorical typical procedure to clarify the complication [12]. Cancer centers should strengthen a management approach that is both clinically adequate and cost-effective, positioned on a superior understanding of the various therapies for extravasation damage [13]. All efforts should be made to reduce the barrier of chemotherapy administration in order to avoid additional side effects of chemotherapy. Every member of the oncology team is responsible for ensuring the safe administration of chemotherapy [2-6]. We check the literature, present clinical data on chemotherapy extravasation, and debate suggestions and guidelines for avoidance and management in this review. This article examines clinical attitudes toward chemotherapy extravasation as well as the most recent approach in the regulation, avoidance, and treatment of chemotherapy extravasation.

METHODS

The writing of the current review article, which includes extravasation of chemotherapy and management of the tissue injury, has been carried out by searching Google Scholar, ResearchGate, and PubMed databases to obtain open-access articles from 2000-2020 of various articles and studies. The key words that have been used were: "extravasation chemotherapy, toxicity, vesicant, extravasation management, antidote to chemotherapy extravasation, Dimethyl sulfoxide, Dextrazoxane, Hyaluronidase."

Exclusion criteria

All citations relating to the extravasation of contrast agents, analgesics, antibiotics, non-chemotherapy vesicant drugs, liposomal cytotoxic drug preparations, parenteral

nutrition, anti-inflammatories, blood products, or proteins were excluded, as were those correlating to the extravasation recall phenomenon, and dermatological harm from systemic therapies. Citations relating to the treatment of ulceration as a result of ineffective extravasation management, surgical debridement, later extravasation, and reporting correlation to the avoidance of skin ulceration after the superficial utilization of cytotoxic drugs were excluded.

Inclusion criteria

Inclusion criteria includes published articles in peer-reviewed journals relevant to extravasation studies, such as clinical trials, review articles, case reports, conferences, and management guidelines.

Classification of I.V Chemotherapy

Drugs administered intravenously are categorized into five groups based on their capability to harm: vesicants, exfoliants, irritants, inflammitants, and neutrals (Table 1) [14]:

Table 1: Categorization of medications used in chemotherapy Regimens [18].

Vesicants	Irritants	Non-Vesicants
<i>DNA-Binding</i>	Bendamustine, Cisplatin, Etoposide, Ifosfamide, Irinotecan, Liposomal Daunorubicin, Melphalan, Methotrexate, Oxaliplatin, Temsirolimus, Teniposide, Trastuzumab, Emtansine, Carboplatin, Fluorouracil, Liposomal Doxorubicin, Mitoxantrone, Topotecan, Aflibercept	Arsenic trioxide, Bleomycin, Bortezomib, Cyclophosphamide, Cytarabine, Eribulin, Gemcitabine, Monoclonal antibodies, Pentostatin, Raltitrexed, Asparaginase, Cladribine, Fludarabine, Paclitaxel, Pemetrexed, Thiotepe
Idarubicin, Mitomycin, Carmustine, Dacarbazine, Daunorubicin, Epirubicin, Mechlorethamine, Amsacrine, Streptozocin, Doxorubicin, Treosulphan, Dacarbazine, Dactinomycin		
<i>Non-DNA-Binding</i>		
Vinorelbine, Cabazitaxel, Docetaxel, Trabectedin, Vinblastine, Vindesine, Vinflunine, Paclitaxel, Vincristine.		

1. Vesicants: drugs that, if unintentionally infused into tissue enclosing a vein, can cause tissue necrosis or blister formation. Dactinomycin, doxorubicin, daunorubicin, epirubicin, idarubicin, vinblastine, mitomycin C, vindesine, and vinorelbine are considered vesicants [15]. Vesicants can be divided into two types: DNA-binding drugs and non-DNA-binding drugs. Alkylating agents and anthracyclines, such as mechlorethamine and bendamustine, are examples of DNA-binding drugs that can cause more severe tissue damage. Non-DNA Vinca alkaloids and taxanes are the most common binding compounds [16].

2. Exfoliants (with minimum vesicant capability): Drugs that are sources of irritation and shedding of skin (peeling off) beyond causing subcutaneous tissue necrosis. Drugs can cause apparent tissue bruises, blisters, and

other side effects. Cisplatin, aclacinomycin, liposomal doxorubicin, docetaxel, mitoxantrone, oxaliplatin, and paclitaxel are among them [17].

3. Irritants: they are agents that can produce inflammation, discomfort, or irritation at the place of extravasation but do not cause blister formation. These agents (e.g., bendamustine, bleomycin, carboplatin, etoposide, teniposide, and topotecan) can produce a burning sensation in the vein after an intravenous infusion [15].

4. Inflammitants: these are medications that produce low-to-tolerant inflammation, painless erythema of the skin, and a flare reaction at the location of extravasation. methotrexate, bortezomib, 5-fluorouracil, and raltitrexed are among them [15].

5. Neutrals: they are characterized as drugs that do not cause inflammation or damage when they are extravasated [14]. This group includes bevacizumab, asparaginase, bleomycin, bortezomib, cetuximab, cyclophosphamide, cytarabine, eribulin, fludarabine, gemcitabine, ifosfamide, melphalan, rituximab, and trastuzumab [15].

Manifestations in Clinical Settings

Chemotherapy extravasation can result in a number of problems, ranging from mild to severe, including acute burning, pain, and swelling at the infusion site. The intensity of the symptoms varies according to the extent and concentration of the substance that has been extravasated. The irritation and erythema, regional soft tissue stiffness, and skin pigmentation progress over a few days or weeks and may result in the formation of blisters [19]. Further structures may be attacked and obliterated as a result of blister formation or necrosis. Depending on the location of the vein where extravasation occurs, damage to nerves, tendons, and joints may occur. Extravasation can be classified into five severity categories based on the clinical significance of the harm produced by anticancer medicines, as represented in Table 2 [19].

Table 2: Degree of clinical severity caused by extravasation of chemotherapy

Grade	Clinical Presentation
1	No symptom
2	Erythema along approximate symptoms, such as edema, phlebitis, pain, induration
3	Ulceration or necrosis, serious tissue damage, operation mediation determined
4	Life-threatening repercussion, crucial interference indication
5	Death

Classification of Extravasation Injuries

Extravasation causes a variety of adverse outcomes, ranging from modest erythema to skin sloughing and necrosis. The symptoms include tingling, itching, burning sensations, penetrating pain, and early induration (Figures 1 and 2).



Figure 1: Erythematous complication after 5 days from doxorubicin extravasation.



Figure 2: Major tissue necrosis of the dorsum of the hand.

In Figure 3A, early symptoms such as swelling, edema, erythema, sloughing, and blistering are demonstrated. Ulceration and tissue necrosis may eventually be late indications (Figure 3B) [20].



Figure 3: (A) Early prediction of extravasation: vesicles; (B) Large-scale ulcer after one week of anthracycline extravasation.

Aspects of Chemotherapy-induced Extravasation Injury

Exposure-induced injury is influenced by the chemotherapeutic substance used, iatrogenic reasons, the patient, and equipment considerations. Numerous features of chemotherapeutic treatment, including the

vesicant's characterization, concentration, volume, and duration of extravasation, all contribute to the risk of extravasation [21].

Chemotherapeutic agent factors

Chemotherapeutic chemicals have been shown to account for a variety of aspects, including their ability to accurately bind to DNA, their ability to suppress dividing cells, their pH, osmolality, diluent properties, and their propensity to produce tissue or vascular dilatation [21].

Patient factors

Numerous characteristics might be included as patient considerations, including small and fragile veins, brittle skin, and age: children and the elderly are more likely to have small portable veins, as well as vena cava obstruction (increased venous pressure can result in leakage) [18]. Patients who are unconscious, confused, medicated, or have communication difficulties may be incapable of addressing pain or discomfort caused by the cannula's position or lowering sensation [21]. Patients with co-morbid conditions that can result in diminished feeling or poor circulation, such as peripheral vascular disease, diabetes, cerebral vascular danger, Raynaud's disease, or obesity, may also experience diminished sensation or poor circulation. Depending on the agent, coexisting medications such as anticoagulants, analgesics, anti-fibrinolytics, vasodilators, hormonal therapy, diuretics, steroids, antihistamines, and intravenous antibiotics may increase blood circulation, predispose patients to bleeding, decrease inflammatory feedback, and decrease pain sensation, among others [22]. Patients with cancer may be at an increased risk due to lymphedema, prior therapy (e.g., mastectomy), long-term treatment adverse effects (e.g., peripheral neuropathy), previous extravasation damage site, and extensive investigations (e.g., blood tests).

Equipment factor

Inadequate dressings or cannula fascination, as well as improperly implanted Central

Venous Access Devices (CVAD), can be identified as the primary equipment factors contributing to extravasation [21].

Iatrogenic factors

The iatrogenic factors include a lack of staff training, insufficient options for the size of the cannula, and insufficient site selection. Extravasation can develop as a result of an unintentional vein puncture or change of the cannula itself as a result of the patient's movement or apprehensive fixing. Longer peripheral line vesicant infusions increase the risk of extravasation, and vesicants should not be infused as unsupervised long-term infusions over a peripheral vein [18]. These factors include inferior selection of location for cannulation, such as the anti-cubital fossa, that may increase the hazard of a high volume extravasation or may have an effect on the harshness of the damage; troublesome or various attempts at cannulation that raise the risk of a consecutive extravasation; for the administration of chemotherapy, steel cannula must not be utilized; the cannula size; the use of a preexisting cannula, and high flow pressure.

Avoidance of Extravasation

Maximum extravasations can be avoided by following systematic administration procedures that are accurate, regulated, and evidence-based. Extravasation risk can be minimized by combining workers involved in the infusion and administration of cytotoxic medications. They must be qualified to implement a variety of preventative measures. If an extravasation occurs, keep in mind that the type of agent, the concentration of the drug, the location of the extravasation, and the length of time a drug establishes its potential for harm all contribute to the degree of injury [18].

Extravasation-related Symptoms of Commonly used Drugs

Anthracyclines

When combined with other chemotherapeutic agents, anthracyclines such as doxorubicin,

daunorubicin, epirubicin, and idarubicin have an intriguing vesicant potential. While many chemotherapeutic agents cause similar extravasation symptoms, anthracyclines are notable for inducing severe pain and a burning feeling that can last for hours. Lesions develop gradually over weeks and widen over months as a result of extravasant vesicants being retained in the tissue [14]. For weeks following the extravasation incident, the surrounding tissue may be red, hard, and painful. The extravasation range's size has an effect on the resolution of redness. If the range of motion is restricted, the redness will gradually fade away over the next few weeks. However, if there is enough extravasation, the redness's interior will become necrotic and unpleasant. Anthracycline leakage might result in serious tissue damage due to cellular absorption and prolonged halting in tissue [23–25].

Taxanes

Paclitaxel and docetaxel are taxanes and are most frequently classified as vesicants in the literature, albeit this is not a valid classification. Tenderness, erythema, and edema are the most frequently reported responses to taxane extravasation [16]. There are case reports of patients who have necrosis and peeling of the skin [27,28]. Taxane extravasation is uncommon and rarely requires surgical debridement. In a research that linked 35 case reports, only three individuals developed ulcers, two of whom required skin closure [26].

Oxaliplatin

Platinum agents are considered irritants. Oxaliplatin has lately been detected to have a vesicant characterization [14]. Extravasation is commonly expressed by palpable swelling and pain upon palpation [14]. Commonly, the lesion evolves into erythematous painful lesions that feature erysipelas. Healing is normally the long-term outcome; surgical debridement and necrosis are rarely needed. The damage from the extravasation of

oxaliplatin is not proportionate to that of anthracyclines and vinca alkaloid [29].

Vinca alkaloids

Vincristine, vinblastine, and vinorelbine are called vinca alkaloids, and their extravasation can result in explicit cellular harm. Extravasation is a well-established cause of predominantly painful ulcers, slow healing, and local paresthesia [14]. It may induce severe agitation, and patients frequently report of agonizing pain near the intravenous site. Erythema and pain in the vicinity of the line or port site may be delayed by 1-2 hours or even three days [30]. Blisters, induration, and edema develop as a result. Sloughing, ulceration, and necrosis of the tissue can all obfuscate the situation. Additionally, vinorelbine, a moderate vesicant, is employed. This results in frequent irritation, which can be avoided with optimal dilution, a precise infusion period, and the use of a sufficiently sized vein [30].

Management of Chemotherapy-induced Extravasation Injury

Every 5 to 10 minutes, continuous monitoring is required at the start and during the infusion. Cancer centers should make sure that "Extravasation Kits" are available at the treatment units. Removable syringes and cannulas, gauze pads, cold-hot packs, gloves, adhesive plaster, and antidotes that can be utilized in extravasation cases, as discussed below, should be included in these kits (Table 3) [4]. Management based on EONS and ONS, as well as a slight accessibility to clinical research, are defined underneath.

First-line Therapy (non-pharmacological treatment)

In the event of chemotherapy extravasation, the first step should be to stop the infusion immediately if the patient complains of pain or swelling, preserving the cannula or port needle in place.

Table 3: Various methods of management for extravasation of different chemotherapies.

Extravasated Drug	Recommended antidote	Stage of evidence	Instruction
Anthracyclines	Dexrazoxane, which neutralizes anthracyclines, is suggested antidote that have been licensed for the treatment of the issue.	Biopsy approval for anthracycline extravasation has been applied in clinical trials.	3-day regimen; Day 1 (within 6 hrs of extravasation) and Day 2 1000 mg/m ² . Day 3 500 mg/m ² .
Anthracyclines	Topical DMSO (99%) is used due to its feature as powerful free radical scavenger that can be applied for preventing tissue ulceration.	Recommended as an applicable antidote in various literature sources.	Used on the site of extravasated tissue immediately. Repeat every 8 hrs for 7 days Discontinue if blistering appears.
Mitomycin C	Topical DMSO (99%) is used due to its feature as powerful free radical scavenger that can be applied for preventing tissue ulceration.	Recommended as an applicable antidote in various literature sources	Used on the site of extravasated tissue immediately. Repeat every 8 hrs for 7 days Discontinue if blistering appear.
Vinca alkaloids	Hyaluronidase decomposes hyaluronic acid ("cement") in soft tissue, leading to diffusion of the extravasated drug, as a result lowering the local concentration of the damaging chemical and elevates its absorption.	Recommended as an applicable antidote in various literature sources.	150–1500 IU s.c. around the site of extravasation.
Taxanes	Hyaluronidase decomposes hyaluronic acid ("cement") in soft tissue, leading to diffusion of the extravasated drug, as a result lowering the local concentration of the damaging chemical and increases its absorption.	Recommended as an applicable antidote in various literature sources.	150–1500 IU s.c. around the site of extravasation.

Following this, attempts are made to aspirate the chemotherapeutic drugs and remove the port needle or cannula [4]. The drug is typically aspirated using a 10 mL syringe for percutaneous needle aspiration [4,31]. If no antidotes are required to be infused at the extravasated site, the catheter can be removed. The altitude of the damaged limb should be followed by thermal application with one of two cold or hot packs [32]. Increasing limb assistance in extravasated drug reabsorption by lowering capillary hydrostatic pressure during the first 24 to 48 hours of the episode [31].

It is also recommended that thermal application be done four times per day for 20 minutes for 1-2 days [33]. Furthermore, saline dispersion can aid in vesicant diluting by infiltrating normal saline through a large catheter. Taking a photo of the extravasation place aids in the monitoring of evolution or healing [31]. Cold compresses can be utilized

to ease pain and local inflammation by causing vasoconstriction and limiting agent transmission. While cold compresses should not be used as a result of vinca alkaloids extravasation because they may cause more tissue injury, warm compresses and heat can be used [15].

Pharmacological Therapy

Dexrazoxane hydrochloride

Dexrazoxane is a member of the bisdioxopiperazine family and is an FDA-approved antidote for anthracycline-induced liver injury. The exact mechanism through which it mitigates chemotherapy-induced extravasation damage in tissue is unknown. Dexrazoxane is administered intravenously (IV) during a period of 1-2 hrs for three consecutive days via a large diameter vein in a leg different than the diseased one. Dexrazoxane has an overall efficacy of 98% and evidence level III-B (Evidence Level III:

Data from well-designed controlled studies without randomization; "B": conservative degree of recommendation) [35,36].

Hyaluronidase

Hyaluronidase is an enzyme that degrades hyaluronic acid in tissues and promotes the diffusion of extravasated agents. A common dose is five 0.2 mL subcutaneous injections of hyaluronidase at a concentration of 150–100 IU [33,34]. It is recommended particularly for vinca-alkaloids, etoposide, and taxane-induced extravasation and has level V-C evidence (Level V evidence: Evidence from systematic reviews of descriptive and qualitative experiments; "C": Suggestion with limited power) [21,35,36].

Dimethyl sulfoxide (DMSO)

Dimethyl sulfoxide is an organosulfur solvent that is applied topically to aid in the absorption of extravasated solvents [31]. Additionally, it exhibits anti-free-radical properties [4]. It has been shown to be effective in a few studies. Cassagnol *et al.* conducted a prospective study in which patients with anthracycline extravasation received 99% DMSO, twice daily for 14 days without developing ulcers [4]. Bertelli *et al.* discovered that one patient out of 122 significant patients who had doxorubicin, mitomycin, epirubicin, cisplatin, mitoxantrone, ifosfamide, carboplatin, or fluorouracil extravasation had an ulcer [37]. Treatment with DMSO was previously regarded appropriate, with the only adverse effects being mild local burning and breath odor [38]. It is utilized as a topical application of 99 percent DMSO at a concentration of four drops per 10 cm² to replicate the extravasation range. In the case of anthracycline extravasation, the combination of DMSO and cooling is frequently recommended as the first line treatment, particularly when dexrazoxane is not practicable [4,23]. Level IV-B evidence (Evidence Level IV: Strongly constructed case-control and cohort studies; "B": cautious recommendation strength) [35,36].

Sodium thiosulfate

This is a common antidote for (nitrogen mustard) mechlorethamine-induced extravasation. Doellman *et al.* discovered that using sodium thiosulfate was associated with substantially enhanced healing time in 63 patients who had a range of chemotherapy-convinced extravasation damages, including epirubicin, vinblastine, doxorubicin, and mitomycin C. It has level V-C evidence [31] (Evidence Level V: Evidence from systematic reviews of descriptive and qualitative studies; "C": Poor strength of recommendation) [35,36].

DISCUSSION

Extravasation is characterized as the unintentional administration of cytotoxic chemotherapeutic medications that are capable of causing severe soft tissue injury, necrosis of the afflicted area, blister development, or sloughing into adjacent extravasated tissues rather than the intended circular channel [39,40]. Extravasation happens at a rate of 0.01 to 7.0% every day. The critical factor in achieving effective prevention of chemotherapy-induced extravasation is consistent training and knowledge of all members of the health team regarding chemotherapy administration, which is accomplished through the provision of current institutional policies and practical training procedures [35,41,42]. Although healthcare personnel and practitioners make every attempt, extravasation of chemotherapy can nevertheless occur during the administration process [35,42]. Statistically, cytotoxic drug extravasation at the time of administration is uncommon, accounting for 0.01–7% of all chemotherapies [35]. However, Wengstrom and Marguiles (2008) asserted that when cytotoxic drug extravasation is compared to other chemotherapeutic side effects, such as GIT disturbance, neutropenic sepsis, and mucositis, the absolute occurrence of extravasation issues falls within a significant range as a result of inappropriate extravasation treatment, which may result in nerve damage [35,43]. This large discrepancy

is apparent because iatrogenic damage is commonly untreated or under-recognized. Additionally, the absence of a precise mechanism for monitoring chemotherapeutic extravasation events contributed to the paucity of reported data. The true occurrence rate is most likely close to the observed spectrum's minimal level [21,33]. Numerous studies assert that the issue is decreasing in prevalence, most likely as a result of improved chemotherapy administration procedures, early diagnosis of cytotoxic medication leaks, and management education. Additionally, a retrospective analysis determined that overall prevalence was tenfold lower in 2002 than it had been for the previous 15 years. With knowledge on extravasation, only a few central venous access devices are available. Froiland [21] estimates that the incidence is between 0.3 and 4.7%. Despite the fact that the specific prevalence of extravasation associated with the use of venous access ports is unknown, the risk of extravasation is expected to be lower when chemotherapies are administered via ports rather than intravenously [44]. Extravasation of implanted devices can be facilitated by a variety of circumstances, including the use of insufficient needles to facilitate access to the port device, poor device fixation, improper positioning, and puncture of the Huber needle [35]. Numerous drugs, including topical and injectable corticosteroids, have been suggested in the literature for the pharmacological therapy of extravasation. Additionally, additional medicines have been advised, including heparin, antihistamines, lidocaine, and sodium bicarbonate, but none of these have been acknowledged as an effective therapy [45]. Despite the fact that natural products such as alpha-tocopherol, *Ginkgo biloba*, and granulocyte macrophage colony stimulating factor have been shown to be effective in the treatment of extravasation damage, their use in combination with other medications may create difficulties in interpreting clinical results [46]. Both topical and parenteral steroids have been postulated to be useful in the therapy of extravagated tissues, although there is a dearth of empirical evidence to support this assertion [45-47].

Local cooling (ice packs) is proposed as a treatment for chemotherapy extravasation using DNA-binding vesicants, and this technique investigates its influence on blood channel constriction, thereby preventing the vesicant from spreading to nearby tissues. On the other hand, local warming is utilized to facilitate the extravasation of non-DNA-binding vesicants, hence increasing blood flow to the extravasated location and facilitating the distribution and absorption of chemotherapy at wounded tissue. Antidotes' consequences for managing the condition are viewed as contentious, rather than following normal therapy protocols. Additionally, if polychemotherapy extravasation is found, identifying the drug responsible for the condition becomes impossible. Additionally, the use of several antidotes, such as dimethyl sulfoxide, dexrazoxane, hyaluronidase, and sodium thiosulfate, is restricted to the treatment of vesicant and large volume extravasation [48]. Dexrazoxane is a bisdioxopiperazine antidote that has been licensed by the Food and Drug Administration for intravenous anthracycline extravasation [48]. Hyaluronidase is an enzyme that degrades hyaluronic acid in tissues, hence facilitating the extravasation of the extravasated substance [48]. It is largely advised for vinca alkaloids, etoposide, and taxanes-induced extravasation. Dimethyl sulfoxide is an organosulfur solvent used topically to improve the absorption of extravasated solvents. It increases the penetrability of vesicant medicines via the skin, increasing their systemic absorption. Additionally, it has the ability to scavenge for free radicals. The use of topical dimethyl sulfoxide has been shown in prospective investigations to retard the course of anthracycline-induced extravasation and mitomycin C-induced damage [31,49]. It is hypothesized that sodium thiosulfate has a genuine inactivating effect on chlormethine (mustine). It is a frequent antidote for mechlorethamine extravasation caused by (nitrogen mustard). Sodium bicarbonate was supposed to be capable of reducing tissue injury while avoiding DNA-binding vesicant

Material, but it is now believed to be the cause of subcutaneous tissue damage [45,47].

Conclusion

Chemotherapy administration and extravasation prevention are shared responsibilities among medical team members. Patients must be taught on the risks and symptoms associated with their condition. Chemotherapy extravasation avoidance is a significant quality indicator for certification of chemotherapy infusion centers (Quality Oncology Practice Initiative, American Society of Clinical Oncology). International guidelines have been published by the European Society for Medical Oncology and the European Oncology Nursing Society in Europe, as well as the American Society of Clinical Oncology and the Oncology Nursing Society in the United States. While few healthcare institutions adopt their own policies and guidelines for extravasation prevention and control, there is a need for local institutions, training, education, and recommendations. Antidotes should be kept on hand at all institutions that offer intravenous chemotherapy. Despite these safeguards, unanticipated extravasation still occurs, necessitating additional research on antidotes for a variety of substances.

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Conflict of interests

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N/A

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