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Clinical report

Time- and dose-limiting erysipeloid rash confined to areas of lymphedema following treatment with gemcitabine—a report of three cases

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Gemcitabine is a deoxycytidine analog with broad antitumor activity. Its main toxicities include myleosuppression, flu-like symptoms, bronchospasms and mild skin rash. We report three cases, in which the patients developed time- and dose-limiting erysipeloid skin reactions confined to areas of impaired lymphatic drainage after application of gemcitabine. Three patients with metastatic tumors (breast cancer, endometrial cancer and non-small cell lung cancer) received weekly infusions of gemcitabine (1000 mg/m^2). All patients suffered from lymphedema of different origin and developed an erysipeloid erythema 40–48 h after chemotherapy within their pre-existing lymphedema. Genuine erysipela was ruled out by laboratory tests and clinical observation. The skin reaction was repeatedly observed and faded after 14 days without specific treatment. Although the pathogenesis of the observed reaction is unclear, it is suspected that the skin symptoms were caused by gemcitabine or its metabolites. Gemcitabine is usually metabolized fast and excreted renally. In areas with impaired lymphatic drainage pharmakocinetics might be altered: inactivation happens slower and the drug might accumulate in the s.c. and cutaneous tissue, thus increasing local toxicity. Clinical judgement and biochemical parameters can help to tell apart genuine erysipela and the erysipeloid reaction. [© 2000 Lippincott Williams & Wilkins.]

Key words: Erysipela, gemcitabine, lyphedema, skin toxicity.

Introduction

The deoxycytidine analog gemcitabine (2′2′-difluorodeoxycytidine) is a nucleoside analog and cytostatic drug with broad activity against solid tumors and hematologic malignancies. After application as a prodrug, intracellular phosphorylation by deoxycytidine kinase is essential for gemcitabine's cytotoxic activity. As a consequence monophosphates, diphosphates and triphosphates inhibit DNA polymerase and ribonucleotide reductase, and thus terminate DNA elongation.[1–3]

Toxicity includes myelosuppression, gastrointestinal reactions, and liver and renal function impairment. Bronchospasms, cardiac symptoms and flu-like reactions have been reported.[4] Skin toxicity has been observed but is usually transient and mild, and appears as skin rash, accompanied by itching and responding to local therapy. Few cases of generalized desquamation have been described.[4]

Here we report three cases in which severe skin reactions after gemcitabine were observed, which appeared to be time- and dose-dependent, and simulated erysipelas. All skin reactions were strictly confined to areas of impaired cutaneous lymphatic drainage.

Case reports

Three female patients, 57, 61 and 65 years old were treated in our department with gemcitabine for different metastatic solid tumors.

All of them were suffering from impaired lymphatic drainage: one had idiopathic lymphedema of both legs, the second had had an abdominal lymphonodectomy (Wertheim–Meigs) with lymphatic edema of the lower belly and thighs, and the third had recently undergone an osteosynthesis of the femur because of a pathologic fracture.

Tumor histologies included non-small cell lung cancer, endometrial cancer and breast cancer. All patients received standard dosage of gemcitabine for the first time (1000 mg/m^2 i.v. weekly; 30 min bolus administration), preceded by 5 mg tropisetrone (Table 1).

At 40–48 h after application all three patients

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Table 1. Patient characteristics and clinical/biochemical findings

Patient/sex/age	no. 1/female/61 years	no. 2/female/57 years	no. 3/female/65 years
Disease	metastatic NSCLC	metastatic endometrial cancer	metastatic NSCLC and breast cancer
Onset of rash	48 h after application	40 h after application	48 h after application
Dosage of gemcitabine	1000/m^2 day 1, 8, 15 (1800 mg abs.)	1000/m^2 day 1, 8, 15 (1600 mg abs.)	1000/m^2 day 1, 8, 15 (1900 mg abs.)
Localization of skin reaction (and cause of edema)	Scar region of thigh (edema after osteosynthesis)	Pelvis and thighs (lymphedema after lymphonodectomy of iliac nodes)	Idiopathic lymphedema of both legs
C-reactive protein (normal $<$0.5 mg/dl)[a]	1.46 mg/dl	0.1 mg/dl	0.49 mg/dl
White blood cells (normal 4000–9500/μl)[a]	7920/μl	2500/μl	4570/μl
Body temperature (oral measurement)[a]	$<$37.5°C	$<$37.5°C	$<$37.5°C

[a]Obtained at onset of erythema.

developed an impressive erythema, redness and warmth with a visible erysipeloid margin within their pre-existing lymphedema (Figure 1).

At first sight bacterial erysipela was suspected. To confirm the clinical diagnosis laboratory tests were performed (C-reactive protein and white blood cells) but none of them revealed pathological values. Other important clinical symptoms of erysipela were missing, too: none of the patients suffered from malaise, fever and chills or pain in the affected limb.

Antibiotics were prescribed in one case because of the extremely suggestive clinical aspect, but showed no action. Local therapy (cooling, local disinfectants) remained ineffective.

After repeated application of gemcitabine the skin reaction developed reproducibly within the same body surface area.

We tried to influence the erythema by reducing the dose of gemcitabine to 75% and observed that the intensity of the skin reaction was dose-dependent; redness and warmth were less impressive after reduction. Because the erythema faded very slowly (up to 14 days), chemotherapy regimens had to be postponed and applied in a reduced dose.

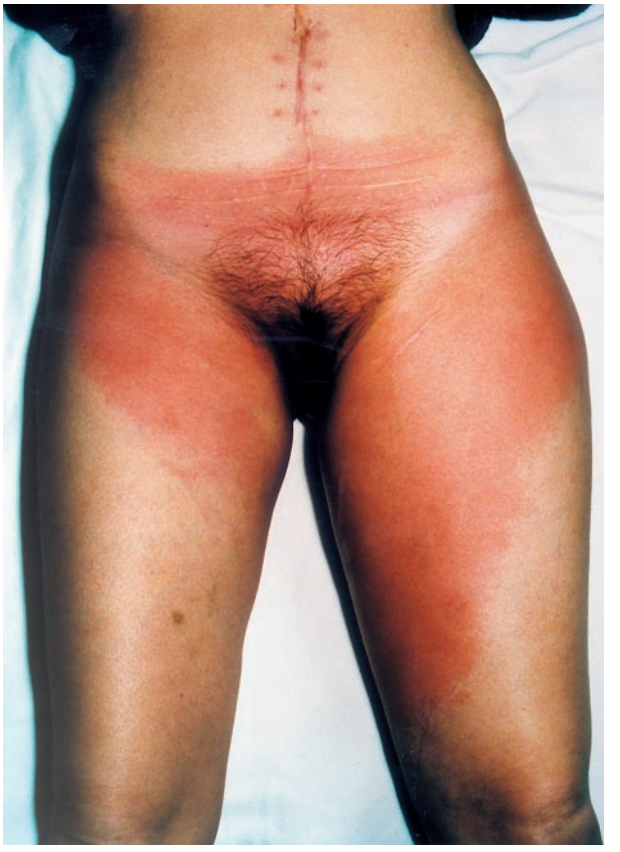

Figure 1. Patient no. 2: 40 h after application of gemcitabine; status after abdominal lymphonodektomy (Wertheim–Meigs): erysipeloid reaction in area of cutaneous lymphatic drainage pathways of resected abdominal lymph nodes.

Discussion

Skin toxicities have been described for gemcitabine but are usually mild. No time- and dose-limiting skin toxicity has been reported before.

We observed three patients with severe erysipeloid erythema after application of gemcitabine. The skin reactions exclusively occurred within pre-existing lymphedema and were difficult to distinguish from erysipela. Although the pathogenesis of this adverse reaction is still unclear, it is suspected that the transient symptoms were caused by gemcitabine or its metabolites.

It is difficult to tell apart the observed skin reaction and genuine erysipela. Tumor patients are prone to

develop severe skin infections because of immunosuppression and frequent lymphedema due to lymph node dissection, metastatic lymph node involvement or radiation therapy. Therefore it is necessary to rule out florid erysipela, as it can be dangerous and lead to streptococcal gangrena or parainfectious glomerulonephritis unless therapy with penicillin G is started soon. Clinical and biochemical findings helped to exclude the suspected diagnosis: erysipelas are characterized by fever and pain as well as elevation of serum parameters of inflammation (C-reactive protein elevation, leukocytosis, elevation of neutrophils in the differential).

All of these clinical symptoms and laboratory findings were not observed in our patients; skin lesions which are typical 'ports' for bacteria were not found, either.

As the skin reaction was restricted to the lymphedema of each patient, we suggest that altered pharmacokinetics of gemcitabine within the lymphedema might be responsible for the erysipeloid rash.

Today it is known that the skin lymphatic system consists of the initial lymphatics, which converge into lymphatic precollectors, collectors and lymphatic ducts; these in turn convey the lymph to regional lymph nodes. Interstitial fluid and particles enter the initial lymphatics through interendothelial openings and by vesicular transport. In particular, lipophilic drugs can overcome these obstacles and be delivered to the lymphatics.[5,6] Lymphedema is characterized by excessive fluid (water, electrolytes and lipid) retention in the interstitial tissue as a result of imbalanced capillary filtration, diffusion and drainage.[7,8]

Normal pharmacokinetics of gemcitabine are well documented; following infusion the maximum plasma concentration is reached after 15 min and is proportional to the total dose administered.

The plasma half-life is short (about 17 min) with a high clearance into central and peripheral compartments.[9] Plasma protein binding is negligible. No data on the lymphotropic potential of gemcitabine are available yet, but the drug is lipophilic and thus has favorable permeant characteristics. This pharmacokinetic profile suggests that permeation into interstitial tissue fluid and consecutive delivery to the lymphatics should be easily possible.

In the animal model it could be demonstrated that injection site drainage of lymphotropic particles and uptake in regional lymph nodes after s.c. administration is drastically reduced in lymphedema.[10] We suggest that drainage of gemcitabine or its metabolites might also be altered in lymphedema.

In addition it is known that metabolization of gemcitabine takes place intracellularly and extracellularly by cytidine deaminase to the inactive difluordeoxyuridine (dFdU) which is excreted almost completely in the urine.[11] In contrast to the parent compound, dFdU has a plasma half-life of 65 h and there are still measurable concentrations of this metabolite after 1 week. Deamination and inactivation takes place mainly in the large organs (e.g. liver).

Subcutaneous tissue might not be able to inactivate the active metabolite adequately and thus be exposed longer to the active metabolite than other body areas.

These three factors (lymphotropy, impaired drainage and prolonged inactivation of the drug) can contribute to an increased exposure of especially cutaneous and s.c. tissue to gemcitabine in patients with lymphedema.

In conclusion the described skin toxicity was dose-limiting and lead to postponement of chemotherapy cycles in the patients observed. Although chemotherapy with gemcitabine is usually well tolerated, clinicians caring for cancer patients with accompanying lymphatic edema must be alerted to this type of adverse skin reaction.

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