

ORIGINAL ARTICLE

Toxic erythema of chemotherapy following i.v. BU plus fludarabine for allogeneic PBSC transplant

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I.v. BU plus fludarabine is an effective conditioning regimen for myeloid neoplasias with low treatment-related mortality. At standard doses, cutaneous toxicity has been reported in <5% of cases. As we observed a much higher incidence of cutaneous toxicity in patients who received predominantly pharmacokinetically based doses of BU, we performed a retrospective analysis of 61 patients who received i.v. BU plus fludarabine (+/- antithymocyte globulin; ATG) as a conditioning regimen before allogeneic PBSC transplant. Of the 58 evaluable patients, 33 (57%) developed cutaneous toxicity that fell within the spectrum of toxic erythema of chemotherapy (TEC). The median onset of TEC was 22 days and most patients had multiple sites of involvement, with the groin, axillae and palms/soles being the favored sites. In men, scrotal involvement, sometimes severe, was also commonly observed. Initially, allergic reactions to antibiotics, fungal infections and GVHD were also considered until the clinical presentation of TEC became well recognized. In all patients, the skin healed without specific therapy but resolution often required several weeks. This series suggests that TEC is common after BU/fludarabine +/- ATG and it is important for transplant physicians to recognize, particularly as misdiagnosis could lead to inappropriate treatment.

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INTRODUCTION

I.v. BU plus fludarabine (IVBuFlu; +/- antithymocyte globulin (ATG)) appears to be a highly effective conditioning regimen prior to allo-SCT for patients with AML or myelodysplastic syndrome.^{1–5} Several reports suggest that IVBuFlu combines the efficacy of a fully myeloablative regimen with the low treatment-related mortality generally seen with reduced intensity or even non-myeloablative regimens.^{3,4,6} For example, de Lima *et al.*⁴ reported a nonrelapse mortality at 12 months of 3%. The decrease in treatment-related mortality appears to be due to a lower incidence of sinusoidal obstructive syndrome (venoocclusive disease) and severe acute GVHD, with the latter hypothesized to be due to less widespread tissue injury.^{1–5} Compared with other myeloablative regimens, an important advantage of BU-based therapy is the ability to modify the dose of BU based upon the pharmacokinetics of the drug in an individual patient. Because of the efficacy and low incidence of serious toxicity, IVBuFlu +/- ATG has become a popular regimen for patients with myeloid neoplasia.

Although there have been several reports regarding the use of IVBuFlu,^{2,3,5,7–14} cutaneous side effects have been described in only a small percentage of patients receiving standard doses of BU. For example, de Lima *et al.*⁴ reported a 4% incidence of 'hand-foot syndrome'. This is in contrast to our experience, described below, which suggests that the majority of patients develop skin toxicity that falls within the spectrum of toxic erythema of chemotherapy (TEC).¹⁵ TEC is a clinicopathological term used to unify a group of cutaneous toxic reactions following chemotherapy that are characterized by areas of burning or painful erythema most commonly involving the hands and feet, axillae and groin, and less

often, the elbows, knees and neck. These eruptions are self-limited and often resolve with desquamation and postinflammatory hyperpigmentation. The clinical recognition of this entity, previously described by anatomically limited names ('hand-foot syndrome') or histologically obscure terms (eccrine squamous syringometaplasia), is important because it often first presents in the complex 2–4 week period after high-dose therapy at a time when several other processes have to be considered including drug allergy, infection and GVHD.

PATIENTS AND METHODS

All patients between May 2005 and July 2010 who underwent an allogeneic PBSC transplant (PBSCT) with a conditioning regimen that contained IV BU and fludarabine (IVBuFlu) plus or minus ATG were included in this retrospective review. The medical records of these patients were reviewed for descriptions of cutaneous findings consistent with TEC starting from hospital admission through day +100. Patients were diagnosed as having TEC if they met the clinical characteristics outlined in Table 1. Specifically, they were required to have bilaterally symmetric involvement of major body folds (for example, axillae, groin, submammary and under the pannus) with burning or pain. Palmoplantar erythema was attributed to TEC when it was associated with burning and/or pain and there were no other findings consistent with GVHD as well as spontaneous improvement without treatment.

Patient and disease characteristics are summarized in Table 2. The pre-transplant conditioning regimen consisted of fludarabine and ATG based on the regimen described by de Lima *et al.*⁴ In the current study, however, the dose of BU was based on the area under the plasma concentration-time curve calculated via the pharmacokinetics of a test dose of 0.8 mg/kg given several days before the treatment doses, with a goal of 4800 µmol-min for the 4 days of treatment. In cases where the targeted dose was

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significantly higher than the BSA-based dose of de Lima *et al.*⁴ the actual dose was left to the discretion of the transplant physician but was often an average of the two doses. Pharmacokinetic studies based upon a test dose of BU were obtained on all patients after 2006 (51 of 58 patients).

Tacrolimus and mycophenolate mofetil were used for GVHD prophylaxis in patients receiving matched (related or unrelated) donor stem cells (Table 2). The tacrolimus was given via IV infusion starting on day - 2 and the dose was adjusted to maintain a trough level of between 5–15 ng/mL. Mycophenolate mofetil was given at a flat dose of 1000 mg IV every 12 h starting on day - 2. In patients who received partially matched unrelated donor stem cells sirolimus (rapamycin) was used instead of mycophenolate mofetil, maintaining a trough level of 3–12 ng/mL, and MTX was given for two doses at 10 mg/m² × 1 and then 5 mg/m² × 1 on days +1 and +3 after transplantation. All patients received anti-seizure prophylaxis with phenytoin during and 1 day following BU therapy. Other standard supportive care included acyclovir, ciprofloxacin, fluconazole and ursodiol.

RESULTS

From 2005–2010, a total of 61 patients at our institution received an allogeneic PBSCT following conditioning with IVBuFlu plus or

minus ATG. Of those 61 patients, three had skin lesions suspicious for TEC, but as the descriptions were equivocal, these three patients were excluded from the analysis.

Table 1. Summary of clinical and histological findings in TEC

<i>Toxic erythema of chemotherapy (TEC)</i>	
<i>Clinical findings</i>	
Erythematous to violaceous patches or edematous plaques involving primarily the:	
Hands and feet	
Intertriginous zones (for example, axillae, groin, submammary or pannus folds)	
Scrotum	
Neck	
Elbows and knees	
Occasionally, when severe, can involve the majority of the body surface area	
Associated with pain and burning more often than pruritus	
Lesions can develop a dusky hue, petechiae and/or sterile bullae (followed by erosions)	
Desquamation is dry on the palms and soles and moist in the intertriginous zones	
Spontaneous resolution without specific therapy	
Can recur if same or higher dose of chemotherapy administered	
<i>Histological findings</i>	
Atypia (enlarged cell and nuclear size, nuclear pleomorphism) and apoptosis of keratinocytes	
Loss of polarity of epidermal cells and crowding of keratinocytes	
Vacuolar degeneration of the basal layer	
Dermal edema	
Eccrine squamous syringometaplasia and/or eccrine hidradenitis	

Table 2. Patient characteristics and results

<i>Patient characteristics</i>	<i>Values</i>	<i>TEC +</i>	<i>TEC –</i>
Total, no (%)	58 (100)	33 (57)	25 (43)
Median Age, years (range)	45.5 (17–59)	44.7 (19–59)	46.4 (17–59)
<i>Age (years), no. (%)</i>			
10–20	2 (4)	1 (50)	1 (50)
21–30	6 (10)	4 (67)	2 (33)
31–40	7 (12)	6 (86)	1 (14)
41–50	18 (31)	7 (39)	11 (61)
51–60	25 (43)	15 (60)	10 (40)
<i>Sex, no. (%)</i>			
Male	34 (59)	17 (50)	17 (50)
Female	24 (41)	16 (67)	8 (33)
<i>Disease Diagnosis, no. (%)</i>			
AML	42 (73)	24 (57)	18 (43)
MDS	10 (17)	6 (60)	4 (40)
Other ^a	6 (10)	3 (50)	3 (50)
<i>Conditioning regimen, no. (%)</i>			
BU/fludarabine	30 (52)	16 (53)	14 (47)
BU/fludarabine/ATG	28 (48)	17 (61)	11 (39)
<i>Donor characteristics, no. (%)</i>			
Matched related	31 (53)	16 (52)	15 (48)
Matched unrelated	16 (28)	12 (75)	4 (25)
Partially matched unrelated	11 (19)	5 (45)	6 (55)
<i>GVHD Prophylaxis, no (%)</i>			
FK506/MMF	46 (79)	28 (61)	18 (39)
FK506/MTX/Rapa	9 (16)	5 (56)	4 (44)
FK506/MTX	2 (3)	0 (0)	2 (100)
FK506	1 (2)	0 (0)	1 (100)

Abbreviations: ATG = antithymocyte globulin; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; TEC = toxic erythema of chemotherapy. ^aOther includes: myeloproliferative disorder, NOS; chronic myelomonocytic leukemia; CML in lymphoid blast crisis; CML in accelerated phase; CML resistant to imatinib; and ALL.

Table 3. Lesion location and characteristics of toxic erythema of chemotherapy (TEC)

<i>Anatomic site</i>	<i>No. of patients (%) (n = 33)</i>	<i>Clinical characteristics</i>
Groin	14 (42)	Major body folds (including under pannus): erythema that can become dusky, followed by erosions and moist desquamation
Axillae	20 (60)	
Submammary folds	5 (15)	
Scrotum	13 (76) ^a	Burning followed by erythema; if erythema subtle, desquamation may be first clue to its existence
Palms/soles	10 (30)	
Face	5 (15)	
Multi-site	21 (64)	
		Erythema + / – desquamation

In darkly pigmented patients, the erythema may go unnoticed until erosions or desquamation develops ^aThe percentage includes only men (n = 17).

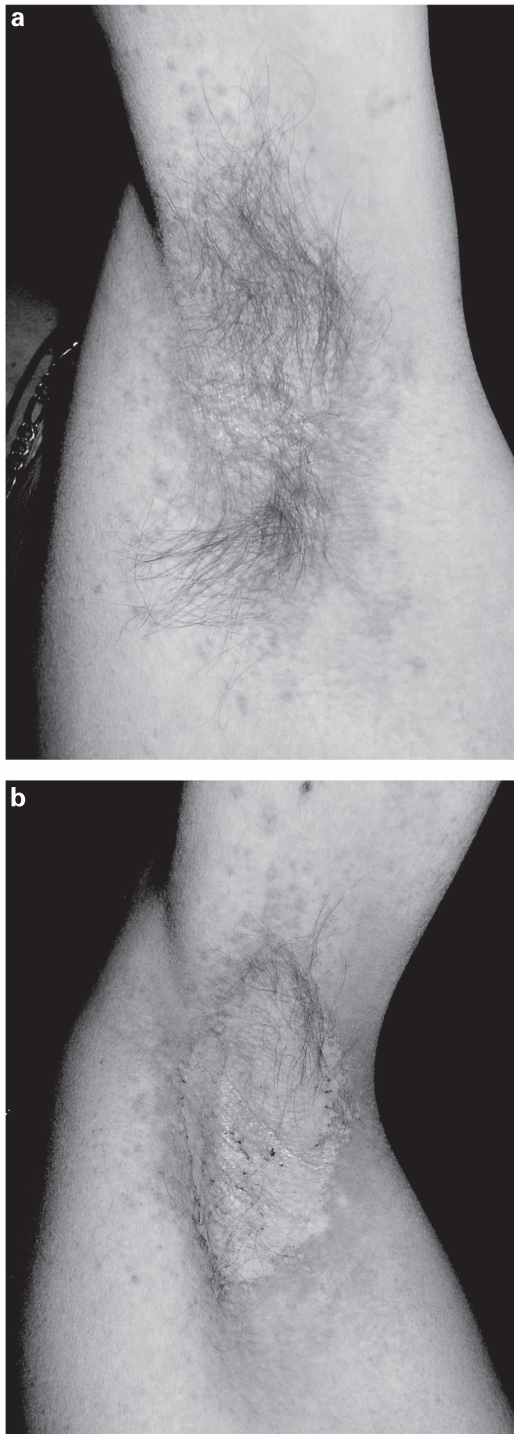


Figure 1. Toxic erythema of chemotherapy. (a) The patient is day +25 following the conditioning regimen of IVBuFlu. There is a thin pink plaque involving the entire axillary vault with a few scattered papules in the surrounding skin. (b) Day +33 with worsening of the eruption in the form of moist desquamation. At this point, given the 1-month time period since the administration of the chemotherapy and the clinical appearance, the misdiagnosis of cutaneous candidiasis or contact dermatitis is made and treatment of either of these conditions is then deemed successful as TEC resolves spontaneously.

Of the 58 evaluable patients, the median age was 45.5 years (range, 17–59 years), with the majority of patients undergoing allogeneic PBSCT for the diagnosis of AML (73%). Patient

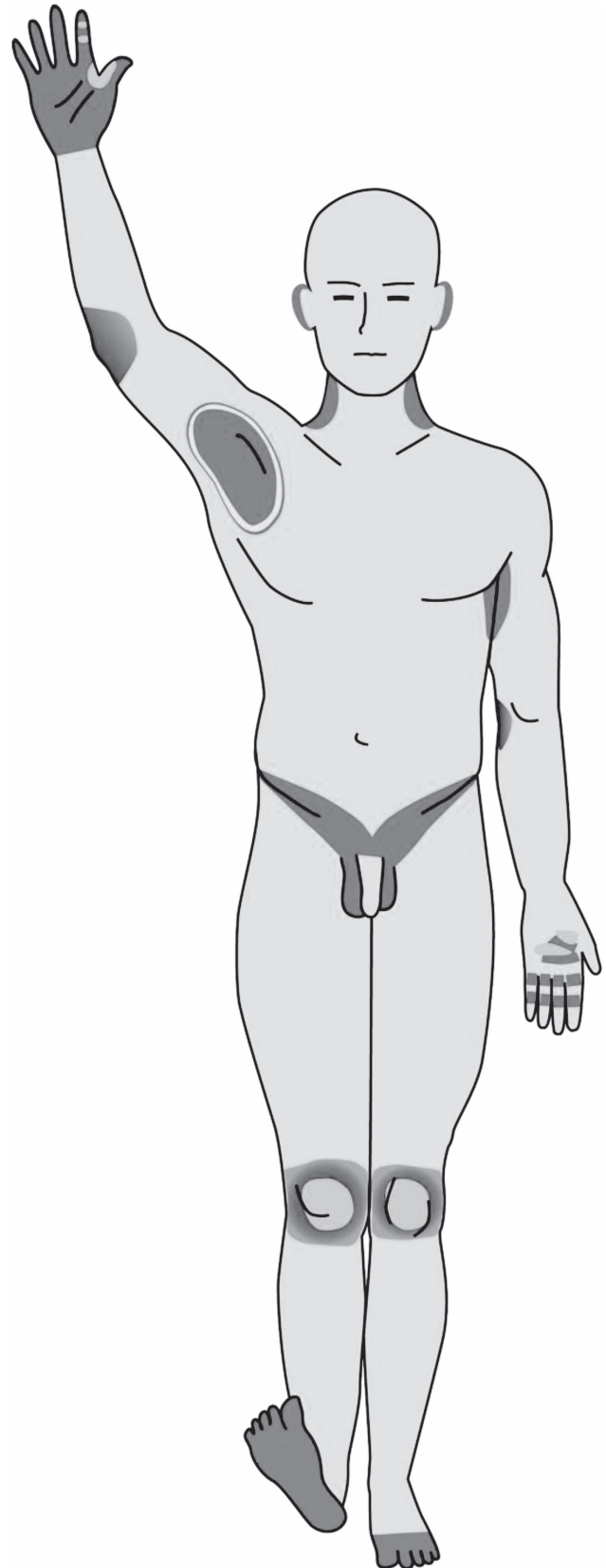


Figure 2. Anatomic distribution of toxic erythema of chemotherapy. The eruption is symmetric and favors the hands/feet, neck, major body folds (for example, axillae, groin and submammary), the scrotum and the elbows/knees. Burning and erythema are seen most commonly, but sterile bullae can form as well. On the palms and soles, the erythema may favor the folds of the fingers.

demographics, diagnoses and transplant regimens are outlined in Table 2. A total of 33 patients (57%) developed TEC (Table 2). The median onset was 22 days following stem cell infusion, with a range from 10 to 35 days. The median duration of TEC could not be consistently assessed based on this retrospective review, but in several patients lasted for weeks and the lesions could worsen over a period of 7–10 days.

Twenty-one patients had multi-site involvement with the most common location being the intertriginous zones (Table 3; Figure 1). The pattern of distribution was symmetric and Figure 2 depicts the favored sites of involvement. The majority of affected men (13 of 17 (76%)) had scrotal involvement. The lesions first appeared as erythematous patches that sometimes became edematous and/or dusky. They were most often heralded by a burning sensation likened to that of a sunburn, with tingling and pruritus being less common symptoms. In major body folds, including under the abdominal pannus, erosions developed as well as moist desquamation. In contrast, acral sites tended to have more dry desquamation. Spontaneous resolution usually occurred over 2–4 weeks, usually with postinflammatory hyperpigmentation in flexural areas.

When the clinicopathological features of TEC were first being defined, the vast majority of patients had dermatological consults, but as the clinical presentation became more familiar, fewer dermatological consults were requested and fewer skin biopsies were performed. In this series of patients, 19 had dermatological consults and four patients who developed TEC had a skin biopsy performed as part of their evaluation. Biopsy results were similar to those previously described (see Table 1).¹⁵ The primary histological features were necrotic keratinocytes and vacuolar degeneration of the basal layer. There was also evidence of epidermal dysmaturation in one patient. None of the patients had spongiosis within the epidermis, as is seen in dermatitis. These histological findings can overlap with GVHD, erythema multiforme and Stevens-Johnson syndrome.

With regard to the conditioning regimen, administration of ATG did not affect the incidence of TEC (see Table 2). In addition, the

type of GVHD prophylaxis regimen (including those with two doses of MTX^{16–18}) did not appear to influence the development of TEC.

DISCUSSION

In contrast to a previous series of patients treated with IVBuFlu,⁴ the majority of our patients developed cutaneous toxicity. In particular, 33 of 58 patients (57%) developed TEC (see Table 2). One potential explanation for the higher incidence of TEC in our patients is that pharmacokinetically based doses of BU tend to be higher than those based upon body surface area.¹⁹ In addition, it is possible that the relatively late onset of TEC obscured the relationship between the conditioning regimen and toxicity. Of note, other BU-containing regimens have been reported to lead to hyperpigmentation in flexural areas and acral erythema²⁰ or a 'rash' with desquamation²¹ (Table 4). The localization of the hyperpigmentation to the flexures suggests that these patients may have had TEC.

A few clinical observations should be mentioned. First, the delayed onset of TEC may lead to erroneous diagnoses including drug hypersensitivity reactions, cutaneous fungal infections (for example, cutaneous candidiasis) and GVHD. For example, palmo-plantar erythema in all of our patients was because of TEC (spontaneous resolution without treatment) rather than GVHD. Second, recognition of the distribution pattern, that is, beyond the palms and soles,^{22–26} allows for a unifying diagnosis rather than a separate diagnosis for each site of involvement. Third, in men, the high incidence of scrotal involvement actually serves as a clue to the diagnosis of TEC, but in the past was often misdiagnosed as candidiasis despite the use of prophylactic anti-fungal medications. Fourth, the natural history of the lesions, that is, spontaneous resolution, may give rise to the false impression that a particular treatment was successful (even for an erroneous diagnosis) or that patients improved because of discontinuation of drug to which they were actually not allergic. Fifth, especially in darkly pigmented patients, the erythema may be subtle and the

Table 4. Reported cutaneous toxicity with BU conditioning regimens for SCT^a

Study (year)	Conditioning regimen	Reported cutaneous toxicity
Morgan <i>et al.</i> ²⁰	Oral BU (4 mg/kg in four divided doses × 4 days) + IV CY (60 mg/kg daily × 2 days) (<i>n</i> = 67)	• Hyperpigmentation of flexural areas (axillae and groin) in 65% of patients • Of those patients, half had flexural erosions • Acral erythema in 15% of patients
De Lima <i>et al.</i> ⁴	IV BU (130 mg/m ² daily × 4 days) + IV fludarabine (40 mg/m ² daily × 4 days) (<i>n</i> = 96)	• 4% of patients (<i>n</i> = 4) had 'hand-foot syndrome' • 5% of patients (<i>n</i> = 5) had a 'rash'
Hoy <i>et al.</i> ²¹	IV BU (dose ranged from 0.8 to 1.2 mg/kg (based upon weight) × 4 days) + IV CY (50 mg/kg/day × 4 days) (<i>n</i> = 28)	• Rash and desquamation in 65% of patients
Perkins <i>et al.</i> ²⁷	IV BU × 4 days with target AUC of 6000 μmol-min (<i>n</i> = 40), 7500 μmol-min (<i>n</i> = 29), or 9000 μmol-min (<i>n</i> = 3) + IV fludarabine (40 mg/m ² × 4 days)	• At AUC of 6000, 20% (<i>n</i> = 4) of patients had grade I dermatitis and 25% (<i>n</i> = 5) had grade II • At AUC of 7500, 21% (<i>n</i> = 6) had grade I dermatitis, 48% (<i>n</i> = 14) had grade II, and 10% (<i>n</i> = 3) had grade III • At AUC of 9000, 33% (<i>n</i> = 1) had grade II dermatitis, 33% (<i>n</i> = 1) had grade III, and 33% (<i>n</i> = 1) had grade IV • The dermatitis was described as hyperpigmentation of skin folds • Grade III and IV toxicity included bullae formation and desquamation

^aThis table contains only the studies that reported cutaneous toxicity associated with a conditioning regimen that used either oral or IV BU. Additional studies evaluating BU were reviewed but did not report on cutaneous toxicity.^{2,3,5,7–14}

development of erosions and desquamation may be the first sign of TEC; the former may be misdiagnosed as herpetic viral infections. Lastly, the duration of the cutaneous toxicity may be weeks and to date, we have found no specific therapy that alters the clinical course.

As the use of pharmacokinetic-based dosing of IV BU is used to target maximal tolerable doses, the incidence of BU-induced TEC may also rise. For example, while the target area under the concentration curve (AUC) in our series of patients was 4800 $\mu\text{mol}\cdot\text{min}$, more recent and ongoing studies are targeting higher AUCs, for example, 6000 $\mu\text{mol}\cdot\text{min}$. A recent publication by Perkins *et al.*²⁷ illustrates this point. Three higher target AUCs were evaluated: 6000, 7500 and 9000 $\mu\text{mol}\cdot\text{min}$. These authors observed a higher incidence of 'dermatitis' than did prior studies that used a lower target AUC (Table 4). Therefore, it is important for hematologists and dermatologists alike to recognize the clinicopathological spectrum of this cutaneous toxic reaction.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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