Toxic Epidermal Necrolysis Associated with TS-1 in a Patient with Gastric Cancer

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A 64-year-old female who has undergone D2 total gastrectomy was started on adjuvant treatment with TS-1. Four weeks after initiation of TS-1, the patient developed a rare complication of life-threatening toxic epidermal necrolysis. TS-1 was discontinued and the patient received treatment with intravenous immunoglobulin and supportive care with resolution of toxic epidermal necrolysis. TS-1 has been used for the treatment of gastric cancer, both in the adjuvant and metastatic setting, and is increasingly being used in other malignancies such as colon, pancreatic and non-small cell lung cancer. TS-1 is generally well tolerated. To our knowledge, this is the first reported case of toxic epidermal necrolysis associated with the usage of TS-1.

Key words: TS-1 – toxic epidermal necrolysis – gastric cancer

INTRODUCTION

TS-1 is an oral fluoropyrimidine that contains tegafur, a prodrug that is converted by cells to fluorouracil (FU); gimeracil, an inhibitor of dihydropyrimidine dehydrogenase which degrades FU; and oteracil, which inhibits phosphorylation of FU in the gastrointestinal tract thus reducing its side effects on the gastrointestinal tract. It has proven efficacy in gastric cancer and is increasingly being used in other cancer types, including metastatic colon cancer (1), metastatic pancreatic cancer (2) and advanced non-small cell lung cancer (3,4). It has a generally tolerable side effect profile.

We describe a 64-year-old Chinese female with Stage III gastric cancer who developed a rare complication of life-threatening toxic epidermal necrolysis (TEN) after 4 weeks of adjuvant TS-1 administration.

CASE REPORT

Mdm Y is a 64-year-old Chinese female who was diagnosed with moderately differentiated adenocarcinoma of the stomach involving the proximal lesser curve as demonstrated on esophagogastroduodenoscopy. She underwent radical D2 total gastrectomy and en bloc splenectomy and final histology showed T3N2M0 disease. This was followed by adjuvant TS-1 (5). Her laboratory results prior to starting TS-1 were as follows: white blood cell 7.67 × 10^9/l, hemoglobin 9.9 g/dl, platelet 695 × 10^9/l, sodium 136 mmol/l, potassium 4.1 mmol/l, creatinine 60 μmol/l, albumin 30 g/l, total bilirubin 5 μmol/l, aspartate aminotransferase 17 U/l and alanine transaminase 13 U/l. Her calculated body surface area (BSA) was 1.56 m^2 and calculated creatinine clearance by the Cockcroft–Gault formula was normal at 81 ml/min and she was prescribed standard dose TS-1 120 mg/day for 4 weeks followed by 2-week rest with no dose reduction. Two weeks after starting TS-1, she was noted to have developed Grade 1 skin hyperpigmentation. She was reviewed by the dermatologist and was treated with skin moisturizer and a tapering 2-week course of prednisolone. TS-1 was continued during this period. A further 2 weeks later, she was admitted to the hospital for worsening skin erosion associated with eye dryness and tearing. She also reported Grade 1 diarrhea for 1-week duration which was controlled with anti-diarrheal medication.

On physical examination, there was generalized skin mottling with background erythema involving the face, which accounted for 4% of total BSA (Fig. 1a), neck (2% of BSA), trunk (6% of BSA), back (18% of BSA) and left lower limb (9% of BSA). There was extensive epidermal denudation (Fig. 1b) especially on the back. Nikolsky’s sign was present...
involving her upper back and left thigh. The patient also had Grade 3 oral mucositis as per the Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 4, with severe pain upon oral intake. Ophthalmological evaluation did not reveal any eye involvement. The patient was afebrile, and laboratory investigations on admission were as follows: white blood cell 0.82×10^9/l, absolute neutrophil count 0.63×10^9/l, hemoglobin 10.3 g/dl, platelet 394×10^9/l, C-reactive protein 141 mg/l, sodium 134 mmol/l, potassium 4.1 mmol/l, urea 10.9 mmol/l, creatinine 86 µmol/l, albumin 37 g/l, calcium corrected 2.4 mmol/l, phosphate 1.15 mmol/l and magnesium 1.12 mmol/l. Urine, stool and blood cultures were negative. Mdm Y was reviewed by a dermatologist and plastic surgeon and a clinical diagnosis of TEN was made with estimated 40–50% BSA involvement. The patient declined skin biopsy. Differential diagnoses included infective causes such as toxic shock syndrome or Staphylococcal scalded skin syndrome (SSSS), but these were subsequently excluded as the patient was afebrile; initial blood, stool and urine cultures were negative; and the patient had involvement of mucous membrane, which was typical of TEN but unusual in SSSS. Apart from TS-1, Mdm Y was not on any other medications except for metformin, gliclazide, hydrochlorothiazide and simvastatin which she has been taking for more than 5 years. TS-1 was deemed to be the offending medication and was discontinued immediately. She scored four points on the SCORTEN scoring system for TEN which predicted a mortality rate of 58%. Her four points were contributed by (i) age over 40 years; (ii) the presence of underlying malignancy; (iii) epidermal detachment involving BSA > 10% on day 1; and (iv) blood urea nitrogen >10 mmol/l. She was treated with intravenous immunoglobulin (IVIG) at a dose of 1 g/kg/day for 2 days starting from day 4 of admission and was supported with daily dressing and intravenous parenteral nutrition. Her course was complicated by worsening of diarrhea to CTCAE Grade 4 requiring intravenous replacement of metabolites and subcutaneous octreotide to control bowel output. Stool investigations did not reveal an infective cause. Both the skin condition and diarrhea improved shortly after the administration of IVIG. She also developed *Klebsiella pneumoniae* bacteremia and *Pseudomonas aeruginosa* urinary tract infection which was treated with intravenous ertapenem. After 6 weeks of hospitalization, she eventually recovered and was discharged, but her performance status deteriorated to ECOG 3 and repeat staging computed tomographic scan showed new liver metastasis. No further anti-cancer treatment was administered and she was treated with best supportive care.

**DISCUSSION**

TS-1, a fourth-generation oral fluoropyrimidine, is an orally active combination drug containing tegafur, gimeracil and oteracil in a molar ratio of 1:0.4:1. It has been used for gastric cancer treatment both in the adjuvant (ACTS-GC) (5) and metastatic (SPIRITS (6), in combination with cisplatin) setting. Increasingly, TS-1 is being used in other cancer types, namely metastatic colon cancer (1), metastatic pancreatic cancer (2) and advanced non-small cell lung cancer (3,4). Grade 2 or 3 skin rash or pigmentation has been commonly reported (1), but no episodes of TEN related to TS-1 have been reported in the English literature.

Cutaneous complications with fluoropyrimidine have been well documented since its introduction. The most common pattern of skin reaction is that of photosensitivity (7), hyperpigmentation (either diffuse, local or serpentine) (7,8), localized hyperpigmentation of irradiated skin (7), inflammation of actinic keratosis (7), exacerbation of seborrheic dermatitis (7), palmar-plantar erythrodysesthesia (9) and rarely TEN. TEN secondary to oral fluoropyrimidine is rare, but has been described in a case report with capecitabine, a third-generation fluoropyrimidine (10). The presentation of the capecitabine case was different from ours, where an African-American man first developed painful macules with crusting over the gluteus and both upper and lower extremities before the skin lesions became generalized.

As TS-1 comprises several active ingredients in a single tablet form, it was difficult to pin-point the exact compound...
that is the causative agent leading to TEN in our patient. The two modulators, gimeracil and oteracil, have not been studied as individual compounds in the clinical setting and it is thus difficult to extrapolate their effects in vivo. However, we do know that hyperpigmentation is one of the common skin reactions in patients treated with 5-FU (7,8). In fact, TS-1 was noted to result in Grade 1 and 2 hyperpigmentation in 48% of the patients in the landmark publication in 2007 by Sakuramoto et al. (5). It might be possible that potent inhibition of dihydropyrimidine dehydrogenase by gimeracil, in our patient, led to a high level of active 5-FU metabolite exposure that eventually resulted in the unusual TEN complication. The temporal sequence of first developing hyperpigmentation, which is common with TS-1 usage, before progressing to TEN in our patient, is suggestive of TS-1 being the causative agent.

TEN is a life-threatening dermatologic emergency associated with 30% mortality (11,12). TEN is most commonly caused by drugs, and the classical culprits are sulfonamides (particularly trimethoprim/sulfamethoxazole), allopurinol, anti-convulsants (phenytoin, phenobarbital and carbamazepine), non-steroidal anti-inflammatory drugs, β-lactam antibiotics and newer drugs, e.g. lamotrigine and tetracapem (11,12). TEN has also been reported with the usage of chemotherapy (capecitabine (10) and docetaxel (13)) and newer biologic-targeted therapies (rituximab (11), imatinib (11) and cetuximab (14)). TEN is defined by epidermal detachment involving >30% of total BSA (15) and commonly involves mucosal surfaces such as conjunctiva, respiratory, oral and gastrointestinal tract. The exact pathogenesis of TEN is yet to be defined but current research has focused on the role of cytotoxic T lymphocytes in the control of keratinocytic apoptosis via death receptor Fas and its ligand FasL (11,12). A clinical scoring system, SCORTEN, has been developed to assess the severity of TEN and to predict mortality (16), and involves the summation of seven clinical variables namely: (i) age over 40 years; (ii) heart rate >120 beats/min; (iii) the presence of cancer or hematologic malignancy; (iv) epidermal detachment involving BSA >10% on day 1; (v) blood urea nitrogen >28 mg/dl (10 mmol/l); (vi) glucose >252 mg/dl (14 mmol/l); and (vii) bicarbonate <20 mEq/l. A patient with 0–1 SCORTEN factors has a low predicted mortality rate of 3%; those with two factors have a predicted mortality of 12%, whereas those with three, four, and five or more factors have high predicted mortality rates of 35, 58 and 90%, respectively. Treatment of TEN includes identifying the offending drug and its discontinuation, management in a burn unit as necessary, aggressive fluid and electrolytes replacement, ophthalmologic review in cases of ocular involvement, appropriate skin care consisting of wound dressing and intravenous antibiotics for superinfection due to skin breakdown. The role of pulse corticosteroid and IVIG remains controversial, although some believe that they should be used early in the disease process (11,12). IVIG is postulated to interfere with Fas–FasL interaction, thus halting keratinocyte apoptosis (12), and was used in our patient.

To the best of our knowledge, this is the first reported case of TEN associated with TS-1 use. In view of the increasing usage of TS-1 in several common cancers, clinicians should be aware of this rare but potentially life-threatening complication.

Conflict of interest statement
None declared.

References