Unexpected outcome (positive or negative) including adverse drug reactions

Cutaneous graft-versus-host disease after proton-based craniospinal irradiation for recurrent Philadelphia-positive acute lymphoblastic leukaemia

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Treatment of recurrent acute lymphoblastic leukaemia (ALL) often involves allogeneic stem-cell transplantation (alloSCT) and disease recurrence in the central nervous system may require craniospinal irradiation. Although graft-versus-host disease (GVHD) is a known risk after alloSCT, cutaneous manifestation within radiation fields is rarely seen. The authors report a case of a 25-year-old man with Philadelphia+ ALL recurring in the central nervous system after a homologous SCT. Craniospinal radiation was delivered with proton therapy to a total dose of 24 cobalt-Gray-equivalents in 12 fractions. Eight weeks after the proton therapy, significant cutaneous GVHD had developed within the radiation fields. This was treated successfully with tacrolimus (4 mg/day), a short course of methylprednisolone, and topical treatment with 0.1% triamcinolone cream, 0.05% clobetasol ointment. Cutaneous GVHD after SCT can be seen within proton radiation fields probably due to an inherent higher skin dose.

BACKGROUND**Introduction**

The treatment of acute leukaemias is challenging, and the outcome of patients varies according to the type of the leukaemia (myeloid vs lymphoid), the presence of cytogenetic abnormalities and the type of therapy. Central nervous system (CNS) involvement at diagnosis or later during the course of the disease is common in patients with acute lymphoblastic leukaemia (ALL). The use of CNS irradiation for prophylaxis in adults with ALL has been modelled after the experience with paediatric patients, in whom use of craniospinal irradiation (CSI) reduces the rate of CNS recurrence from approximately 35% to 10%.^{1 2} Although, prophylactic cranial irradiation is used only rarely in the era of high-dose systemic and intrathecal chemotherapy because of the perception of increased risk of neurologic toxicity and decreased tolerance of systemic therapy after CNS irradiation; its use becomes acceptable with disease recurrence in the CNS which portends a poor prognosis, particularly for adults with ALL who develop CNS recurrence after effective intrathecal chemotherapy.³

Patients for whom primary therapy fails are commonly offered bone marrow or stem-cell transplantation, which in most cases is by necessity from a genetically non-identical donor. More than five decades ago, one of the first such transplants, involving transplantation of splenocytes from a non-syngeneic donor, was noted to induce a severe reaction later known as graft-versus-host disease (GVHD),⁴⁻⁶ an immune-mediated syndrome that remains a major cause of mortality and a common source of morbidity after stem-cell transplants. The incidence and severity of GVHD is related to the extent of genetic mismatch of the donor material and the type of conditioning regimen used.^{7 8}

In contrast to photon therapy, particle therapy, including proton therapy allows for superior sparing of normal tissues distal to the beam. However, there are potential physical and biologic differences between photon and proton therapy. Triggering GVHD in the radiation field is an interesting and clinically relevant finding. To our knowledge we are the first to report of GVHD involving the skin within the radiation portals after CSI specifically using proton therapy.

CASE PRESENTATION

The patient, a 22-year-old Caucasian man with a previously unremarkable medical history, presented to MD Anderson Cancer Center with fatigue, sore throat and fever up to 101.5°F. His white blood cell count was 658 100×10⁶/μL (normal range, 4–11) with 98% blasts, haemoglobin level was 5.9 g/dL (normal 14.0–18.0), platelet count was 37×10³/μL (normal 140–440), lactate dehydrogenase was 6424 U/L and uric acid (4.6 mg/dL) levels. Immunophenotyping, cytogenetics analysis and fluorescence in situ hybridisation of peripheral blood and bone marrow samples confirmed the diagnosis of Philadelphia-positive (Ph+) precursor B cell ALL. The initial treatment consisted of plasmapheresis and cefepime (2 g intravenously every 12 h), allopurinol (300 mg daily), dexamethasone (40 mg intravenously daily) and hydroxyurea (3 g PO twice a day). The patient was then enrolled in an institutional protocol (2006-0478) testing the combination of hyper-CVAD, dasatinib and rituximab (cyclophosphamide 300 mg/m² (total dose 546 mg) intravenously every 12 h for 3 days (six doses), vincristine 2 mg intravenously on days 4 and 11, doxorubicin 50 mg/m² (total dose 91 mg) as a 24-h infusion on day 4, dexamethasone 40 mg on days 1–4 and days 11–14, sodium 2-mercaptopethane

sulfonate (Mesna) 600 mg/m² (total dose 1092 mg) as a continuous infusion for 3 days), dasatinib 100 mg PO once a day for 14 days, and rituximab 375 mg/m² (total dose 683 mg) on day 1). Because his initial lumbar puncture revealed leukaemic blasts, he was also given intrathecal methotrexate 12 mg alternating with cytarabine 100 mg for a total of 12 doses. At the completion of eight cycles of hyper-CVAD with dasatinib, rituximab and intrathecal methotrexate/cytarabine, he was in complete haematologic and cytogenetic remission.

Following six cycles of maintenance therapy (dasatinib (100 mg daily), vincristine (2 mg intravenously on day 1 of each 28-day cycle) and prednisone (200 mg/day on days 1–5), the patient developed transient right hemiparesis, aphasia and mental status changes, blasts were present in the cerebrospinal fluid (CSF), with negative brain MRI. At that time, 1 year after initial diagnosis, bone marrow biopsy revealed recurrent B cell lymphoblastic leukaemia with 71% blasts. He began systemic steroids and biweekly intrathecal chemotherapy, first with methotrexate and then with cytarabine. Systemic therapy consisted of augmented hyper-CVAD off protocol (cyclophosphamide 300 mg/m² (total dose 530 mg) intravenously every 12 h for 3 days (six doses), vincristine 2 mg intravenously on days 1, 8 and 15, doxorubicin 50 mg/m² (total dose 90 mg) as a 24-h infusion on day 4, dexamethasone 80 mg on days 1–4 and 15–18, sodium 2-mercaptoethane sulfonate (Mesna) 600 mg/m² (total dose 1060 mg) as a continuous infusion for 3 days, and PEG-asparaginase 2500 units/m² (total dose 4425 units) intravenously on day 1). The neurologic symptoms resolved completely after two intrathecal treatments, but the blasts persisted in the CSF for more than 3 weeks. After three cycles of augmented hyper-CVAD plus dasatinib, the patient was in haematologic and cytogenetic complete response.

Figure 1 Patient's face 5 weeks after completing radiation showing the severe keratoconjunctivitis and skin erythema secondary to graft-versus-host disease.

Fifteen months after the initial diagnosis, the patient underwent an allogeneic stem cell transplantation (allo-SCT) from his HLA-matched sister using clofarabine and busulfan conditioning. No signs of GVHD were noted and the patient continued to take 2 mg of tacrolimus daily as prophylaxis. Peripheral-blood and bone-marrow chimerism studies on day 30 showed more than 99% successful engraftment: 98% of T cells and 100% of myeloid cells were of donor origin. Cytogenetics analysis showed no evidence of BCR-ABL1 rearrangement, nor was BCR-ABL fusion found by PCR. Intrathecal chemotherapy was continued.

Eighteen months after diagnosis (6 months after the first CNS relapse, and 3 months after the alloSCT), a CSF sample obtained before an intrathecal chemotherapy dose revealed 4000 white blood cells with blasts predominating, consistent with a second CNS relapse of the leukaemia. At that time, twice-weekly intrathecal methotrexate and cytarabine was resumed, as was systemic therapy with methotrexate, cytarabine, dasatinib, rituximab and PEG-asparaginase. After 10 days, the CSF was clear of blasts, and the intrathecal chemotherapy was changed to once a week and then once every 2 weeks. After one cycle, the systemic therapy was changed to vincristine 2 mg in combination with dexamethasone 40 mg PO for 4 days and dasatinib 50 mg PO daily. After two cycles of

Figure 2 Patient's back and scalp showing graft-versus-host disease skin signs 5 weeks after completion of radiation.

systemic therapy, the patient was found to be in complete remission and was referred for consolidation radiation therapy.

At presentation for radiation therapy, the patient was 25 years old, with Ph+ lymphoblastic leukaemia in second complete remission after CNS and bone marrow relapse, with no evidence of disease in the CNS or marrow and ongoing engraftment with his sister's marrow. CSI was planned and delivered using passive scattering proton therapy. Dose was prescribed in CGE (Cobalt gray equivalents) using a relative biologic effectiveness value of 1.1. A total dose of 24 CGE (cobalt-Gray-equivalents) was delivered in 2-CGE fractions over a 2.5-week period (figure 1). Treatment simulation, planning and delivery took place while the patient was supine. Proton therapy was delivered in five fields: left posterior oblique brain, right posterior oblique brain, upper spine posterior-anterior (PA), mid-spine PA and lower spine PA. To decrease the risk of double-treating the junctions of the three

matching fields, each field had three modifications for the initial field and the two subsequent junctional shifts. Radiation was delivered as once-daily fraction without concurrent intrathecal chemotherapy. Although the patient tolerated the treatment well, with no radiation-related side effects during the 2.5-week radiation delivery period, ongoing anaemia required several blood transfusions. Grade 1 erythema, an expected side effect, was noted in the treatment portals at end of the radiation treatment. However, 1 month after the end of radiation treatment, the patient presented with grade 2 conjunctival inflammation, absolute madarosis (loss of eyelashes) and keratopathy (corneal inflammation) without evidence of corneal ulceration, although conjunctival ulceration was present in both the left and right lower eyelids, his vision was 20/25 in right eye and 20/40 in the left eye. At that time lubricating and steroid eye drops were prescribed. He also developed hearing loss along with severe grade 3 dermatitis in both ear lobes.

Five weeks after completion of craniospinal proton therapy (8 months after the alloSCT), the patient developed erythema with fine scale and desquamation limited to the radiation portals (figures 1 and 2).

INVESTIGATIONS

Punch biopsy of the skin revealed a cell-poor interface dermatitis with vacuolar alteration of basal keratinocytes and dyskeratotic keratinocytes along the dermal-epidermal junction. The epidermis was acanthotic with hyperkeratosis and hypergranulosis, and mild spongiosis, supporting the diagnosis of chronic GVHD. Bone marrow biopsy revealed no morphologic evidence of acute leukaemia.

Figure 3 Patient's face 4 months after completion of radiation showing improvement of skin graft-versus-host disease.

Figure 4 (A, B) Patient's back and scalp 4 months after completion of radiation showing improvement of the skin.

TREATMENT

The patient's tacrolimus dose was increased to 4 mg daily; he received a short course of methylprednisolone and topical triamcinolone 0.1% cream, clobetasol 0.05% ointment and hydrocortisone 2.5% cream to apply twice daily to affected areas. The reaction within the radiation portals resolved 10 weeks.

OUTCOME AND FOLLOW-UP

There was a slow but consistent improvement of the skin dermatitis, that went from brisk inflammation to heperpigmented lesions that faded away at the time of this report (figures 3 and 4). As for the eyes the patient's vision continues to be blurred along with mild keratoconjunctivitis and optic nerve blind spot with minimal improvement in his right eye vision. As for his hearing it is back to normal.

DISCUSSION

Allogeneic stem-cell transplants can cause GVHD, an inflammatory syndrome, even when the donor is a sibling who shares the major histocompatibility genes.⁹ The syndrome is prompted by the reaction of the transplanted immune cells to the recipient's tissues and primarily affects five target organs: the skin, gastrointestinal tract, liver, the host's lymphopoietic system and lung.¹⁰ This process can occur acutely, within the first 3 months after the transplant, or chronically at any time after the transplant and is responsible for much of the late morbidity and mortality experienced after alloSCT.

Acute cutaneous GVHD presents as an erythematous desquamating rash that characteristically involves the palms, soles and trunk. Histopathologic evaluation of involved skin may reveal focal or diffuse vacuolisation of the basal cell layer (grade I); satellite cell necrosis (grade II); necrotic keratinocytes with pyknotic nuclei and eosinophilic cytoplasm, often with subepidermal cleft formation (grade III); and finally complete loss of the epidermis (grade IV).¹¹ The pathophysiology of acute GVHD in the skin can be considered as a three-phase process. In phase 1, the conditioning regimen (radiation, chemotherapy or both) initiates damage of the host tissues and evokes secretion of inflammatory cytokines such as tumour necrosis factor- α and interleukin-1 and heat shock proteins. These signals activate resting dendritic cells, enhance the expression of the HLA-DR cell-surface receptor and various adhesion and co-stimulatory molecules, and may stimulate the release of chemokines that can expedite the recruitment of donor T cell effectors into the skin. The infusion of allogeneic stem cells then initiates phase 2, wherein activated host dendritic cells present alloantigens to the donor T cells. The activated donor T cells further stimulate the dendritic cells via co-stimulatory pathways such as CD40: CD40L, which in turn enhance T cell stimulation and clonal expansion. In phase 3, the histopathologic changes of acute GVHD in the skin become apparent when the keratinocytes undergo premature apoptosis.¹⁰

The effects of ionising γ radiation on immune reactions within the skin have been studied. Hofmeister et al used a human skin explant model to show that high-dose γ radiation can activate skin dendritic cells and cause T cell stimulation in mixed lymphocyte reactions.¹⁰ Others

reported on the acute radiation reaction of skin characterised with vasodilatation and increased leakage of albumin and fibrinogen with single doses exceeding 20 Gy. Ullrich and Casserett^{12 13} showed that Cobra Venom factor given before radiation reduced the inflammatory response and significantly reduced the late skin fibrosis. These radiation induced inflammatory response can be a trigger to activate the skin immune system. This could be one explanation for the clinical reports of GVHD exacerbation within radiation portals when external-beam radiation follows stem-cell transplantation. Cutaneous chronic GVHD localised to the radiation fields has been reported after alloSCT.^{14 15} However, to date, all reported cases have involved photon-based radiation.

Here, we report a case of cutaneous GVHD appearing within the radiation portals following treatment of the craniospinal axis with proton therapy. Proton therapy offers the physical advantage of additional sparing of

Figure 5 Sagittal section of the proton treatment plan showing coverage of the brain and spin.

normal tissues distal to the beam edge (figure 5). In contrast to traditional photon based CSI, protons reduce or eliminate unnecessary dose to thyroid, bowel, heart, gonads etc. It is believed that this will ultimately reduce the incidence of secondary malignancies and end organ damage (heart disease). However, the current case demonstrates that cutaneous GVHD may be encountered following proton therapy. While the incidence of GVHD following proton therapy is unknown, it is not unreasonable to think that rates may differ from those seen following photon radiation. Unlike photon therapy, proton therapy, delivered using passive scattering technology, may deliver a relatively high entrance dose to the skin, due to a lack of proximal conformality. In theory, this would be associated with increased levels of radiation-based activation of cutaneous immune cells and potentially an increased incidence of cutaneous GVHD. In contrast to passive scattering, newer delivery modalities, including scanning beam proton therapy may allow for improved proximal conformality and subsequently, lower skin dose. However, there are also biologic uncertainties associated with proton therapy. The relative biologic effectiveness (RBE) value is used to compare the amount of biologic damage induced by differing radiation modalities. Based on historical studies, a generic value of 1.1 is used at most proton therapy centres. However, in reality, RBE is likely a complex factor which varies as a function of radiation dose, fraction size beam energy and cell type.^{16 17} Indeed some groups have found that the RBE for skin, measured *invivo*, may approach or exceed 1.2.¹⁸ The specific RBE for cutaneous immune cells is unknown.

Learning points

- Cutaneous GVHD within the radiation portal is a rare side effect of external-beam radiation therapy, administered using photons, after alloSCT. Proton therapy has distinct physical differences allowing for sparing of normal tissues beyond the beam edge. However, dose to the skin along the beam entry may be higher, and biologic uncertainties exist. The case presented suggests that GVHD following proton therapy should be managed, as is true for all other cases of GVHD, with immune modulation in addition to therapy directed toward symptom relief. Additional studies are needed to determine the incidence of GVHD following proton therapy.

Competing interests None.

Patient consent Obtained.

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