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Enhanced cutaneous radiation effects following high-dose busulfan therapy

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Summary. Fifteen patients received irradiation after combined chemotherapy with high-dose busulfan followed by autologous or allogeneic bone marrow transplantation. Of nine patients irradiated between day 30 and day 70 after their engraftment, seven developed an increased radiation response in the skin: four showed enhanced reactions during irradiation, and three had a total or severe definitive alopecia more than 16 months after CNS irradiation. Six patients were irradiated after day 70; they had either normal reactions or none at all within the cutaneous radiation portals. The possibility that busulfan might be a radiosensitizer is raised.

Introduction

The cutaneous effects of long-term as well as high-dose busulfan therapy are well known: hyperpigmentation, bullous eruption, erythema nodosum, and porphyria cutanea tarda [3–6]. We observed increased cutaneous reactions to radiotherapy delivered soon after high-dose busulfan therapy.

Patients and methods

Since 1983, 33 patients were treated for malignant tumors with busulfan (4 mg/kg per day for 4 days) combined with cyclophosphamide (50 mg/kg per day for 4 days) and/or melphalan (140 mg/m^2) and followed by autologous or allogeneic bone marrow transplant (BMT) at the Institut Gustave-Roussy pediatric department. In all, 15 patients received radiation therapy (^{60}Co, 11; high-energy X-rays, 4) after their engraftment, for either a tumoral residue ($n=11$), central nervous system (CNS) prophylaxis ($n=3$), or supportive antalgic care ($n = 1$). Retrospectively, we studied early and late cutaneous reactions occurring within the radiation portals and their relation to the time lapse between chemotherapy and radiotherapy.

Results

The 15 irradiations began between day 30 and day 188 after BMT, with a median delivered dose of 35 Gy (range, 18–65 Gy). The technique of irradiation was rather uniform: the patients were treated through opposed AP-PA or lateral portals equally weighted and treated the same session. Cone-down boosts were employed to deliver the highest doses. In 14 patients, the dose per day ranged from 1.6 to 2.5 Gy with 4 or 5 weekly sessions. One patient received an accelerated hyperfractionation (0.75 Gy $\times$ 5/day) but did not develop any untoward side effects. All patients had hyperpigmentation before radiotherapy, and seven developed unusually severe early or late radiation effects in the skin.

Three patients with non-Hodgkin's lymphoma received CNS prophylaxes of 18 Gy; for two of them, irradiation began on day 33 and day 54 after BMT. They are both alive, 16 and 20 months after their engraftment, with no evidence of progressive disease, but they have a total alopecia. The third patient began irradiation on day 70 after BMT. She is alive and in complete remission 23 months after her engraftment, but her hair is very sparse and fine. All of the other children who received no CNS irradiation following combined chemotherapy with high-dose busulfan, recovered their normal hair in a median time of 3 months.

Of the other 12 patients, 4 developed increased cutaneous effects during irradiation. One received a total dose of 60 Gy from day 34 after BMT on a residual sinusal rhabdomyosarcoma. At 18 Gy, she showed a very severe reaction in the hemiface with erythema, edema, and ulceration, associated with a dramatic radiomucositis requiring morphinic antalgic drugs. The other patient, with a Ewing sarcoma, received 60 Gy from day 37 after BMT on the sacrum and left femur. At 15 Gy, increased radiation effects appeared in the skin within the radiation portals, with erythema, edema, and bullae, associated with hemorrhagic cystitis. This was quite unusual at this dose level and with the energy used (18-MeV X-rays). These lesions led us to stop irradiation at 24 Gy. The evolution was satisfactory after a 1 week pause, and radiotherapy was completed up to 60 Gy. This cutaneous toxicity is uncommon for these doses. Two children were irradiated on a residual, femoral Ewing sarcoma from day 30 and day 50, respectively, after BMT, with a total dose of 60 Gy. They developed erythema and hyperpigmentation within the radiation portals, which are commonly seen with this type of radiotherapy, but also ulcerations and desquamation, which are less frequent. One of them had precocious radiotherapeutic sequellae with edema and thin skin 3 months later, although a nonirradiated lateral strip of tissue had

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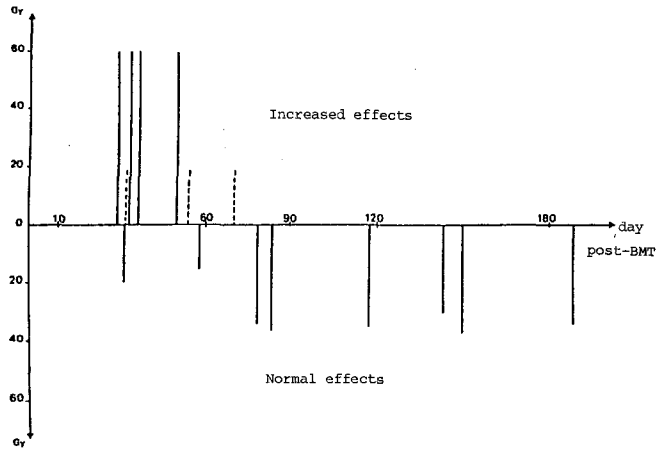

Fig. 1. Relation between time and cutaneous radiation effects following busulfan therapy (———, local irradiation; – – – –, CNS prophylaxis), indicating increased and normal effects on various days post-BMT

provided adequate lymphatic drainage. The other underwent an amputation because of local recurrence.

Eight patients showed either minimal cutaneous radiation effects or none at all. Two children were irradiated before day 70 post-BMT. One received 20 Gy on a mediastinal neuroblastoma residue from day 34. The second child, with a pelvic rhabdomyosarcoma, had local tumoral progression and received, 15 Gy from day 58 as antalgic supportive care. For six patients, irradiation began after day 70 post-BMT (day 78 – day 188). These were local irradiations for tumoral residue on the abdomen, pelvis, and mediastinum, with a median delivered dose of 35 Gy (range, 28–55 Gy).

Thus, all the increased cutaneous radiation effects followed irradiations that began before day 70 post-BMT, as illustrated by Fig. 1.

Discussion

Several cutaneous side effects following busulfan therapy have been described [1, 3–6]. Hyperpigmentation is the most frequent in patients treated with long-term busulfan therapy for chronic granulocytic leukemia and in those receiving bone marrow transplantation after combined chemotherapy with high-dose busulfan. When these patients' skin is studied using light or electron microscopy, toxic effects are observed in the melanocytes, with stimulatory effects on the production of melanin [1] and keratinocyte nuclear atypia in the epidermis [4]. No increased radiation effects have previously been reported after busulfan therapy.

Our data suggest that there is a possible interaction between busulfan and radiation. There are no reports of permanent alopecia following a CNS irradiation of 18 Gy, which is frequently used as a CNS prophylaxis in the treatment of acute lymphoblastic leukemia or lymphoma in children. Such definitive alopecia are only described after higher doses of radiation therapy of >35 Gy, given for CNS tumors. In addition, we did not observe increased effects in the cutaneous radiation portals when combined chemotherapy with high-dose cyclophosphamide or melphalan was followed by radiotherapy. Not all of the patients in this study developed enhanced reactions in the skin, but the occurrence of such side effects seemed to be linked with the time lapse between chemotherapy and radiotherapy.

Enhanced radiation responses in the skin are well known for certain drugs: adriamycin, actinomycin D, bleomycin, 5-FU, and hydroxyurea [2, 7]. Such increased cutaneous effects appear when chemotherapy and radiotherapy are concommitant or when irradiation is carried out prior to chemotherapy. The peculiarity of the present study is that the radiotherapy was delivered at least 30 days after combined chemotherapy with busulfan.

Other clinical observations and radiobiological studies are necessary to examine a possible radiosensitizer effect for busulfan and to explain the mechanism of interaction between ionizing radiations and a drug known to induce nuclear lesions in skin cells.

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