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Low-dose radiation therapy for steroid resistant Kasabach-Merritt syndrome

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ABSTRACT

From 1990 to 2001, a total of five hemangioma patients with Kasabach-Merritt syndrome received radiation therapy at Tohoku University Hospital. Steroids were administered before, during and after radiation therapy to all of the patients and interferon-α was administered to two patients. Radiation therapy was administered with a 4 MV X-ray was in four patients and a 12 MeV electron in one patient. Planned target volume included hemangioma with a 1-2 cm margin in all directions. A radiation dose of 3-3.5Gy was administered in 3-5 fractions. Rapid and transient increase of platelet count was observed in three patients. In two patients, an additional course of radiation was administered and the second course of radiation seemed to be effective for both. Of the three patients with hemangioma of the extremities, growth inhibition of irradiated extremities was not observed, and, in fact, elongation of extremities was observed in two patients. In one patient, lymphangioma developed from irradiated hemangioma. Although no serious late complications were observed in our series, 3-3.5Gy of radiation therapy for KMS seems to be insufficient to obtain rapid and stable improvement of thrombocytopenia.

Key words : Kasabach-Merritt syndrome, Radiation therapy, Low-dose

INTRODUCTION

Kasabach-Merritt syndrome describes thrombocytopenia accompanied by large hemangioma[1]. KMS is sometimes fatal[2] and requires treatments such as steroid[3),4)], surgery[5], embolization[6], anticancer drugs[7),8)], interferon[9], and radiation therapy[3),4),9)-12)]. Radiation therapy is mainly used for steroid-resistant

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cases and has been shown to reduce the mortality. In the literature, a total dose of 6-16 Gy given a series of in 1-2 Gy fractions seems to be the standard radiation therapy and has been reported to be effective in 57%-100% of the patients[10)-12)]. However, late complications of radiation therapy such as growth delay of irradiated extremities or atrophy of muscles have also been reported[13)-15)]. In our institution, we have used small radiation doses for the treatment of Kasabach-Merritt syndrome to avoid late complications in newborn patients. In this study, the treatment outcomes of small dose radiation therapy (3-3.5 Gy in 3-5 fractions) are investigated.

MATERIALS AND METHODS

Patients

From 1989 to 2001, a total of five hemangioma patients with Kasabach-Merritt syndrome received radiation therapy at Tohoku University Hospital and its affiliated hospitals. The clinical course of these patients was investigated by reviewing clinical records. In all patients, KMS developed within 2 months after birth. The hemangiomas were located in the neck (n=1), in the flank (n=1), an upper

Table 1. Patients and treatment characteristics.

Case	Age	Gender	Tumor location	Size of hemangioma (cm×cm)	Combined therapy	Radiation therapy	Re-irradiation	Observation period	Complication
1	2 mo.	male	left neck	4×4	steroid	3.5 Gy/5 fractions using 4 MV X-ray	no	9y6m	no
2	2 mo.	female	left flank	9.5×5.5	steroid, compression, INF α	3.5 Gy/5 fractions using 4 MV X-ray	no	2y8m	no
3	3 mo.	female	left thigh	9×9	steroid, compression, INF α	3 Gy/3 fractions using 12 MeV electron	3 Gy/3 fractions using 12 MeV electron	8y7m	Limitation of hip joint motion, elongation of extremity, lymphangioma
4	5 days	male	right thigh	5×4	steroid	3 Gy/3 fractions using 4 MV X-ray	no	14y	elongation of extremity
5	2 days	male	left arm	5×4	steroid, compression	3.5 Gy/5 fractions using 4 MV X-ray	5.5 Gy/5 fractions/5 days using 4 MV X-ray	12y2m	no

extremity (n=1), and in the lower extremities (n=2). The size of hemangiomas ranged from 4 ×4 cm to 9.5x5.5cm.

Treatment

Steroids were administered before, concurrently, and after radiation therapy in all of patients and interferon-α was administered in two patients. The decision to treat with methods other than radiation therapy was determined by pediatricians, but indications and methods of radiation therapy were determined by radiation oncologists. Radiation therapy was administered by a 4 MV X-ray in four patients and a 12 MeV electron in one patient. The planned target volume included the hemangioma with 1-2 cm margin in all directions. To avoid treatment failure due to body motion, sedation was performed in every treatment session. The patients and treatment characteristics are listed in Table 1. To improve DIC (disseminated intravascular coagulopathy), gabexate mesilate was administered to all patients.

RESULTS

Survival

In the observation periods from 2 years 6 months to 14 years of age, all five patients are now surviving and platelet count is normal in all of the patients.

Clinical course of five patients after radiation therapy

Case 1

No significant increase in platelet count was observed after 3.5 Gy/5 fractions/ 5 days. However, the hemangioma size decreased gradually in the subsequent 3 years and the platelet count recovered to a normal range. It is unclear if radiation therapy was effective for this patient.

Case 2

Rapid increase in platelet count was noted soon after the start of radiation therapy, however, the increase in platelet count was temporary. During the period of steroid administration after radiation therapy (predonisolone, 6-15 mg/kg body weight over 3 months), the size of hemangioma at the left flank slowly decreased and platelet count gradually recovered.

Case 3

Rapid increase in platelet count was noted soon after the start of radiation therapy (3.5 Gy/ 5 fractions/5 days) followed by redevelopment of thrombocytopenia after completion of radiation therapy. Forty-three days from the start of the first course of radiation therapy, the patient was reirradiated was with the same dose. After reirradiation, platelet count increased rapidly and thrombocytopenia was alleviated. Hemangioma regressed significantly after second irradiation. Seven years later, lymphangioma developed from residual hemangioma. This patient is now undergoing regular checkups for lymphangioma as an outpatient.

Case 4

After radiation therapy (3 Gy/3 fractions/5 days), a transient rapid increase in platelet count followed by a slow but permanent increase in platelet count was observed.

Case 5

The first course of radiation (3.5 Gy/5 fractions/5 days) was not effective, thus patients were reirradiated (5.5 Gy/5 fractions/5 days) 21 days after the start of first irradiation. After second radiation therapy, the hemangioma lost its glossy appearance and became soft and wrinkled. Platelet count recovered

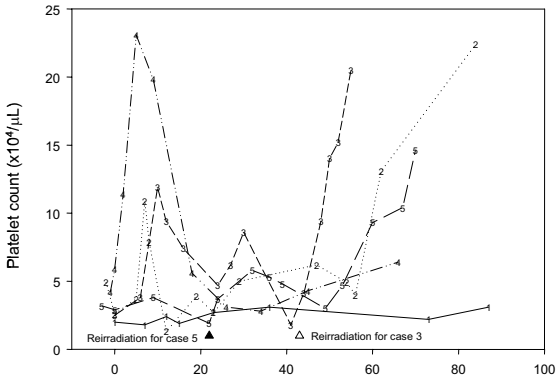

Fig. 1.
The changes of platelet count after radiation therapy.

concomitantly with changes of tumor appearance.

The changes of platelet count after radiation therapy are plotted in figure 1.

Complications

Of the three patients with hemangioma of extremities, elongation rather than growth inhibition of extremities was observed in two patients. In one patient, lymphangioma developed from irradiated hemangioma.

DISCUSSION

KMS is treated by steroid[3),4)], surgery[5)], embolization[6)], anticancer drugs[7),8)], interferon[9)], and radiation therapy[3),4),9)-12)]. Among these methods, radiation therapy is used as a second-line therapy mainly for non-responders to steroid therapy primarily due to late complications such as growth inhibition[13)-15)]. Despite reports of complications, the effectiveness of radiation therapy for KMS has been established by many manuscripts. According to el-Dessouky et al., it appears that radiotherapy alone or in combination with steroids gives a superior overall treatment in terms of reducing the death rate[2)]. Shin et al. recommended treating KMS with a stepwise multimodal approach i.e. steroid followed by radiation therapy and then by IFN-alpha[10)]. We also use steroids as the first-line therapy and radiation therapy as a second-line therapy.

Although radiation therapy has been shown to be effective for KMS, dose and fractionation varies widely from report to report and optimal radiation dose has not been determined. Mitsuhashi et al. treated 7 KMS patients using 8-10 Gy in 8-10 fractions and reported a response rate of 57% (4/7)[11)]. Shin et al. used 6 Gy in 3 fractions and reported effectiveness in 21 of 28 patients (75%)[10)]. Ogino et al. reportedly treated 8 KMS patients, with a success rate of 100%, with 6-16 Gy in 3-10 fractions[12)]. Schild et al. treated two Kasabach-Merritt syndrome patients, one with 6.25 Gy in 3 fractions and another with 14 Gy in 8 fractions[13)]. They reported that radiation therapy was effective for both of these patients. In summary, from radiation doses 6 to 16Gy, given are commonly to treat KMS.

To avoid late complications of radiation therapy, we have been treating KMS with small radiation doses(3 Gy in 3 fractions-3.5 Gy in 7 fractions). It was difficult to evaluate effectiveness of radiation therapy in our series, because none of the five patients revealed a rapid and permanent increase in platelet count after first course of radiation therapy. However, an eventual stable recovery of platelet count to over 10^6/ml was obtained in 3 of 5 patients, one after single course radiation therapy and two after two courses of radiation therapy. Although the criteria for effectiveness differ in the literature, our treatment outcome may be inferior to the other reports[9)-13)]. The recovery of platelet counts after 3-3.5 Gy of radiation therapy appears unsatisfactory. Since both of

the two patients who received a second course of radiation therapy showed stable recovery of platelet count, a larger dose of radiation than that used in our series seems to be necessary.

It is well known that radiation therapy for small children causes late complications such as skin dystrophy or growth inhibition of bone and age, thus radiation dose is an important factors[13)-15)]. Relatively small doses of radiation are usually adapted for treatment of KMS. Mitsuhashi et al. reported shortening of extremities in each of three reirradiated patients[11)]. Similarly, Ogino et al. observed muscle atrophy, dislocation of hip joint and shortening of extremity eight irradiated patients,[12)]. Recent reports of complications of radiation therapy for KMS are summarized in Table 2 along with radiation dose and effectivity. In our series, skin dystrophy and shortening of extremity was not observed. On the contrary, elongation of irradiated limb was observed in two patients. However, it is unclear whether this phenomenon is caused by low dose radiation therapy or by the influence of excess blood supply due to hemangioma. In case 3, lymphangioma developed from residual hemangioma seven years after radiation therapy. However, it is also unclear in this case if the development of lymphangioma from hemangioma resulted from radiation therapy or not.

There is a great variation in the reported radiation doses for KMS. In addition, we could not draw a final conclusion about optimal radiation dose in this study, a nationwide dose finding study is necessary to investigate enough number of KMS patients.

CONCLUSION

Although no serious late complication was observed in our series, 3-3.5Gy of radiation therapy for KMS seems insufficient to obtain rapid and stable improvement of thrombocytopenia.

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Table 2. Reported treatment outcomes of radiation therapy for Kasabach-Merritt syndrome

Author	Year	Number of patients	Radiation therapy	Response rate	Complication
Mitsuhashi[10)]	1997	7	8-10 Gy/ 8-10 fractions	4/7 (57%)	Shortening of irradiated extremities in 3 patients (all re-irradiated)
Shin[9)]	2000	28	6 Gy/ 3 fractions	21/28 (75%)	
Ogino[11)]	2001	8	6-16Gy/ 3-10 fractions	8/8 (100%)	Muscle atrophy in two, dislocation of hip joint in one, Shortening of extremities in one.

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