Long-term outcomes of low-dose radiotherapy in Kasabach-Merritt syndrome

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Purpose: Reports on results of radiation therapy (RT) for Kasabach-Merritt syndrome (KMS) are limited. We performed a retrospective study to evaluate the response rates and late complications and to determine the adequate RT dose for patients with KMS patients.

Materials and Methods: We studied 11 patients who received RT between October 1988 and September 2008 for KMS refractory to pharmacologic therapy. All patients had external hemangiomas and received the diagnosis of KMS within 12 months of birth. All 11 patients received steroids as the first-line therapy; eight patients additionally received interferon-α therapy, and one patient underwent surgery. Nine patients underwent single-course RT with a total dose of 4.5–8 Gy (1.5–2 Gy/fraction). Two patients received multiple courses of RT, with a cumulative total dose of 12 Gy (2 Gy/fraction) and 18 Gy (1.5 Gy/fraction), respectively.

Results: The median follow-up period was 156 months (interquartile range [IQR], 75 to 226 months). The median total dose of RT was 6 Gy, and all patients maintained complete remission until the last follow-up. An additional course of RT was performed for refractory cases or cases of local relapse after initial RT. Rapid platelet count increase after RT was seen in most patients, which returned to normalcy in a median of 20 days (IQR, 5 to 178 days). However, seven patients experienced radiation-related long-term complications.

Conclusion: Low-dose RT is effective and yields rapid response in patients with KMS. However, given growth-related late complications, RT should be carefully considered.

Keywords: Kasabach-Merritt syndrome, Radiotherapy, Hemangioma, Thrombocytopenia, Treatment outcome, Adverse effect

Introduction

Kasabach-Merritt syndrome (KMS) is a rare disease usually occurring in infants or young children that manifests rapidly growing vascular tumors, thrombocytopenia or consumptive coagulopathy. KMS typically presents 2 types of hemangiomas: tufted angiomomas (TA) and kaposiform hemangioendotheliomas (KHEs). KMS was first reported by Kasabach and Merritt in 1940. However, its incidence remains low, accounting for 0.3%–1% of all vascular tumors. Hemangiomas in KMS typically develop in the upper and lower extremities, trunk, perineum, and the head and neck region. In particular, the mortality rate increases up to 10%–37% cases where the primary lesion is located on vital organs or where treatment response is poor.

Treatment options for KMS include pharmacologic therapy (steroids, interferon [IFN]-α, vincristine, sirolimus, propranolol), radiation therapy (RT), surgery, and embolization. Although the most effective treatment option remains unclear, pharmacologic treatment is frequently used to avoid late toxicities. Steroid can often be a mainstay for first-line therapy, while vincristine and sirolimus can also be combined in the first-line. Surgical excision is mainly used only for small, localized lesions owing to the hemorrhage risk.
associated with vascular tumors [11].

Several case reports indicate that RT yields effective therapeutic response in KMS [8,12-16]. However, RT is often deferred as the salvage option owing to substantial concerns regarding late toxicities in younger patients with KMS [8,13,14]. However, only a few studies have evaluated response rates or late toxicities and the adequate RT dose through serial observation. Therefore, this study aimed to assess the response rates and late complications with RT and determine the optimal dose of RT in patients with KMS.

Materials and Methods

1. Patients

We retrospectively reviewed the medical records of 11 patients with KMS who received RT at our institution between October 1988 and September 2008. The Institutional Review Board of Seoul National University Hospital (IRB No. 2109-007-1250) approved the study and waived the requirement for informed consent.

Table 1 summarizes the patient characteristics. Of the 11 patients, five were boys and six were girls. All patients had tumors located externally as follows: the head and neck (n = 5); extremities (n = 3); flank (n = 1), buttock and inguinal (n = 1), axilla, and chest and lip (n = 1). KMS was diagnosed based on a rapidly growing hemangioma and accompanying thrombocytopenia (platelet count \(< 150,000/\text{mm}^3\)) or consumptive coagulopathy. Hemangioma was typically diagnosed based on gross appearance or imaging studies (ultrasonography, magnetic resonance imaging, and/or computed tomography). KMS was diagnosed by the age of 12 months in all patients. Only 3 patients underwent biopsy; it was not routinely performed for diagnosis.

2. Treatment

At our institution, combination therapy is preferred for KMS. We consider total resection if the patient has small and localized tumors at diagnosis or after pharmacologic treatment. Otherwise, steroid therapy (prednisone: 2 mg/kg body weight) is initiated for 2 weeks. Response to steroid therapy was evaluated using hematology tests and physical examination or imaging studies. IFN-α (300 \(\times 10^4\) IU/m² per day) and/or RT was additionally performed in patients with no significant reduction in hemangioma size and with sustained thrombocytopenia or with persistent coagulopathy. Although combination therapy is the preferred treatment at our institution, individualized treatment was offered according to the patient’s tumor size, tumor location, age at diagnosis, and hematology status.

Table 2 summarizes the treatment characteristics of all patients who were treated with RT. All patients received steroids as the first-line therapy; eight patients received additional IFN-α therapy and one patient underwent mass excision. The median steroid therapy duration was 7 months (interquartile range [IQR], 2 to 11 months); it was continued after RT for all patients except one (patient #2).

With regard to RT, nine patients received a single course of RT, and the total dose was 4.5–8 Gy (1.5–2 Gy/fraction). Multiple courses of RT were performed for two patients—total cumulative doses: 12 Gy (2 Gy/fraction) and 18 Gy (1.5 Gy/fraction). In total, two patients were treated with \(^{60}\text{Co}\) γ-rays, six patients with a 4–6 MV photon beam, and three patients with a 6–12 MeV electron beam. The RT target volume only included hemangioma, excluding skin lesions such as purpura or ecchymosis around the tumor. RT was delivered using a two-dimensional radiotherapy (2D) technique for most patients, and intensity-modulated radiotherapy

### Table 1. Summary of the characteristics of 11 patients with Kasabach–Merritt syndrome

| Case no. | Sex | Age at diagnosis | Tumor location                  | Presentation                      | Histology                              | Initial platelet count (\(\times 10^4/\text{mm}^3\)) |
|----------|-----|-----------------|---------------------------------|----------------------------------|----------------------------------------|-----------------------------------------------|
| 1        | M   | 7 months        | Lt. cheek                       | Mass with DIC, respiration difficulty | ND                                    | 20                                            |
| 2        | M   | 2 months        | Rt. flank                       | Mass with thrombocytopenia       | ND                                    | 13                                            |
| 3        | M   | 9 months        | Lt. thigh                       | Mass with DIC                   | ND                                    | 13                                            |
| 4        | F   | 9 days          | Lt. lower leg                   | Mass with thrombocytopenia       | Hemangioendothelioma                  | 6                                             |
| 5        | M   | 3 months        | Lt. buttock and inguinal        | Mass with thrombocytopenia       | Tufted angioma                        | 28                                            |
| 6        | F   | 1 month         | Rt. face and neck               | Mass with DIC, vomiting, hematuria | ND                                    | 9                                             |
| 7        | F   | 9 months        | Lt. temporal bone area          | Mass with thrombocytopenia       | Hemangioendothelioma                  | 97                                            |
| 8        | F   | 2 months        | Rt. neck and shoulder           | Mass with DIC                   | ND                                    | 16                                            |
| 9        | F   | 3 months        | Rt. arm                         | Mass with DIC                   | ND                                    | 13                                            |
| 10       | F   | 9 months        | Lt. axilla, chest, and lip      | Mass with thrombocytopenia, respiration difficulty | ND                                    | 9                                             |
| 11       | M   | 4 months        | Lt. occipital area              | Mass with thrombocytopenia, hematochezia | ND                                    | 35                                            |

DIC, disseminated intravascular coagulation; ND, biopsy was not done.
(IMRT) was applied additionally for one patient (patient #5) who received multiple courses of RT.

Results

The median follow-up duration was 156 months (IQR, 75 to 226 months). Table 3 summarizes the treatment outcomes of 11 patients. Fig. 1 shows the change in platelet counts after RT. No significant treatment response was observed after first-line pharmacologic therapy in any patient. Four patients did not show any response to treatment, and two patients showed disease progression even after combination therapy with steroids and IFN-α.

Before RT, the size of the hemangiomas ranged from 2.5 cm to 25 cm in diameter. Of patients who underwent single-course RT, seven achieved complete remission from the hemangioma (Fig. 2); the tumor nearly disappeared on imaging in one patient (patient...
Fig. 1. Changes in platelet counts after (A) single course and (B) multiple courses radiotherapy (RT).

#6), and in one patient, although residual tumor remained, its size decreased (patient #7). Two patients underwent multiple courses of RT: one patient (patient #2) had refractory disease to initial RT and one (patient #5) had local recurrences after complete remission and underwent two additional RTs. One patient (patients #5) showed marked tumor regression after the second RT and underwent mass excision. However, the second local recurrence occurred 3 months after surgery. Additional RT was performed, and complete remission was achieved 2 months after the third RT.

A total of 11 patients achieved normal platelet counts after RT. The median time to achieving a normal platelet count was 20 days (IQR, 5 to 178 days). Eight patients (72.7%) had a significantly elevated platelet count within 1 month after the first course of RT. Furthermore, all patients with coagulopathy showed complete hematologic remission after RT. Patient #4 showed a relatively late response; however, the platelet count gradually increased and normalized 2 years after RT. Patient #2 had no significant response after the first course of RT with regard to both platelet count and tumor size. This patient underwent RT 1 month later, which successfully increased the platelet count to the normal range, and the hemangioma significantly reduced in size. Patient #5 showed complete remission from the tumor after the first RT and the platelet count normalized; however, the platelet count decreased at each local recurrence of hemangioma. The platelet count showed an increasing trend with each additional RT and normalized after the third RT.

Radiation-related long-term complications were identified in seven patients. Of all patients with sequelae, leg-length discrepancy was observed in two patients who were treated with multiple courses of RT (Fig. 3). Among patients with leg-length discrepancy,
Discussion and Conclusion

Hemangioma is the most common congenital lesion, with an incidence of 5% among infants [17]. Typically, infantile hemangioma is a benign tumor that develops during the first few weeks of age and shows characteristic growth patterns and spontaneous regression. Most infantile hemangiomas do not require treatment. However,
functional abnormalities or life-threatening conditions caused by hemangioma require treatment [18]. KMS is a hemangioma-related disease that requires treatment. Hematologic abnormalities associated with KMS, including severe thrombocytopenia, can be potentially life-threatening. In particular, KMS has been reported to be associated with specific hemangiomas (KHE and TA) and not common infantile hemangiomas [19,20]. In the present study, among the three patients who underwent biopsy, two had KHE, and one had TA.

Although several treatment options exist for KMS, evaluating the effectiveness of each treatment modality is challenging because most studies reported treatment outcomes using combination therapy [12,13]. In this study, all patients were treated with a combination therapy including RT.

Steroids are the most commonly used first-line therapy for hemangiomas and play an important role in their treatment. Although the mechanism underlying the therapeutic effect of steroids is not fully understood, they are known to contribute to the inhibition of angiogenesis and fibroblast proliferation. Although the response rate with steroids against common hemangiomas is excellent (90%), it is inferior (30%–50%) in KMS [14,21]. Treatment response onset occurs typically within 1–2 weeks after steroid therapy starts. In case of no response or KMS relapse, a second-line agent should be considered. In our study, all patients received steroids as the first-line treatment, and eight patients received steroids combined with IFN-α 1–2 weeks after steroid therapy was started.

According to previous studies, IFN-α is an effective second-line or combination agent for KMS [12,14,22-24]. IFN-α exerts its antiangiogenic effect by inhibiting endothelial cell and fibroblast proliferation [25]. Hesselmann et al. [14] reported successful therapeutic outcomes using a combination therapy with IFN-α and RT for a patient with a life-threatening condition non-responsive to steroids. However, not all patients respond to IFN-α, and IFN-α also poses a risk of neurological toxicities. Greinwald et al. [26] reported complete remission in 42% and no response in 16% of 24 patients with massive or life-threatening hemangiomas treated with IFN-α. In addition, they observed neurological toxicities in 26% of the patients.

Vincristine and sirolimus are emerging as new alternative first-line treatments for KMS. With regard to the mechanism of action, vincristine is known to promote apoptosis of endothelial cells, and vincristine is generally used in combination with systemic steroids [27]. Several recent studies have reported excellent therapeutic efficacy of vincristine for KMS [28-30]. Wang et al. [30] reported clinical outcomes from 17 patients with KMS treated with combination therapy, and treatment responses to steroid and vincristine were observed in 35.5% and 80% of patients, respectively. Sirolimus, which functions by inhibiting endothelial proliferation and promoting vascular stability, presents a treatment option for complicated vascular malformations and hemangiomas, including KMS [31,32]. A prospective study comparing the treatment outcomes of vincristine and sirolimus in KHE and high-risk vascular tumors is currently in progress.

Complete surgical resection, if possible, is the most effective method to resolve hematologic abnormalities caused by hemangiomas. However, surgery presents a significant risk of bleeding associated with the highly vascular and infiltrative characteristics of KMS. Therefore, surgical intervention can be selectively performed for localized tumors that have decreased in size at the initial diagnosis or after pharmacologic therapy [11,33].

Radiosensitivity of hemangiomas has been reported since 1940. Historically, RT has been used as the most effective treatment for hemangiomas. In the first case report of KMS by Kasabach and Merritt [1], the patient was treated with RT and showed excellent treatment response. Several studies have demonstrated an excellent response of KMS to RT (60%–100%) [8,12-16]. Shin et al. [12] reported their outcomes with 37 patients treated using a stepwise multimodal approach. The steroid-only group had an 11% response rate, and the steroid and RT combination group had a 75% response rate. In addition, Leong and Bydder [16] reported successful treatment of two patients with life-threatening KMS non-responsive to other treatments, with RT. These results show that RT could be an attractive treatment option for KMS refractory to other treatments.

The platelet counts can indicate tumor regression in KMS and could be a useful surrogate for surveillance after treatment in KMS [8,13]. Previous studies have reported three cases of RT wherein the platelet counts increased rapidly after RT and normalized after 7–40 days [8,16]. This study included 11 patients, whose platelet counts were closely associated with the course of the disease and returned to normalcy in a median time of 20 days after RT. RT response evaluation using platelet counts can be recommended approximately 1 month after treatment. Furthermore, after remission of coagulopathy, RT achieved long-term disease control with complete response basis tumor size and platelet counts.

The optimal radiation dose described for KMS treatment varies in the literature. The reported total cumulative dose ranges from 5–41.2 Gy [8,13]. Schild et al. [34] reported a higher rate of complete response in patients with large hemangiomas treated with cumulative doses of 25–30 Gy, as compared to lower doses. Other studies have recommended a maximum total dose of 10 Gy to minimize long-term complications [13]. In the present study, the median total dose for patients who achieved a complete response was 6 Gy (range, 4.5 to 18 Gy). All nine patients who underwent single-course RT received a total dose of less than 6–8 Gy. These results suggest that 6–8 Gy could be an adequate dose for patients
responding to initial RT.

However, several studies have reported late adverse effects of RT in infants [8,13,14]. These concerns have led many physicians to overlook RT as a treatment option for KMS. Mitsuhashi et al. [13] reported the treatment outcomes of combination therapy, including RT in seven patients with KMS. Of those, three patients were treated with a single-course RT, with the remainder being treated with multiple courses of RT. All patients had complete remission; however, extremity shortening was observed in three of the patients who received multiple courses of RT. In our study, RT showed excellent response in all patients, but long-term sequelae were identified in 63.6% of the patients (n = 7). Five patients with sequelae received a cumulative dose of < 10 Gy, with the minimum total dose being 6 Gy. Although a low dose is sufficient to manage KMS, concerns regarding the late toxicities of RT remain. In our study, all patients underwent 2D-RT with a large irradiated field to cover the hemangioma entirely. However, this approach is now outdated, and we expect that using the current RT techniques can help spare normal tissues. Modern imaging modalities and IMRT will contribute to accurate target definition and reduce the organ at risk dose by achieving better conformity, respectively. For example, helical tomotherapy or volumetric modulated arc therapy may enable long bone-sparing holo-limb radiotherapy to reduce the radiation dose for long bones and achieve homogeneous dosing on surrounding soft tissues [35]. Furthermore, adding vincristine and sirolimus to KMS treatment will enable tumor size reduction and subsequently, irradiation volume reduction to minimize late complications of RT. Hence, a review of late complications of RT using current treatment modalities is needed through follow-up studies.

This study has several limitations. First, it was a retrospective, single-institutional study; treatment response and toxicities were not fully evaluated owing to the lack of medical record data. Particularly, assessing the gross tumor reduction rate on time was challenging because the tumor size was not repeatedly measured using imaging at each follow-up. However, physicians confirmed the final response status after long-term follow-up through a physical examination or imaging. Second, the standard treatment for KMS remains unestablished and differs among patients. Finally, this study included a small number of patients given the rarity of KMS.

In conclusion, RT is an effective treatment modality for patients with KMS non-responsive to other treatments. Furthermore, low-dose RT (6–10 Gy) yields excellent and rapid disease control. However, RT could contribute to growth-related long-term complications. Therefore, RT for the treatment of KMS should be carefully considered.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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