Granulocytic Sarcoma: Results of Radiotherapy

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We analyzed retrospectively the patients of granulocytic sarcoma treated with radiotherapy at the Department of Radiation Oncology, Yonsei University College of Medicine from Mar. 1987 to Mar. 1992 in an attempt to review our experience with irradiation of granulocytic sarcoma and to evaluate the treatment results for the radiation dose response.

Fourteen lesions of granulocytic sarcoma in 9 patients were developed in variable clinical settings such as AML, CML and without leukemia. The involved lesions were bone, lymph node, soft tissue and skin in descending order of occurrence. All of the lesions in 9 patients were treated with external beam radiotherapy (Co-60 or electron beam). Both age distribution and clinical settings did not show any correlation with the response to treatment. The response to treatment seemed to be better for lesions in the bone than in other involved lesions. The majority received local irradiation of a total dose of more than 2000 cGy. Radiation dose of more than 2000 cGy showed excellent local control of 100% (11/11), while local contol decreased to 33% (1/3) with total dose less than 2000 cGy.

In conclusion, local radiotherapy seems to be very effective for palliative or curative aim of granulocytic sarcoma, and a radiation dose more than 2000 cGy is highly recommended.

Key Words: Granulocytic sarcoma, Radiotherapy

INTRODUCTION

Granulocytic sarcoma has been defined as a "localized tumor mass composed of immature cells of granulocytic series[1]". It was first described by Burns[2] in 1811 and its association with leukemia was established by Dock[3] in 1893. The term "Chloroma" was originally assigned to this sarcoma by King[4] in 1853 because such tumors often display a greenish color that fades in tumor cells. "Granulocytic sarcoma", the currently prefered term, was first used by Rappaport in 1966[5].

Granulocytic sarcoma has been reported to occur in three clinical settings: 1) as a harbinger of acute myelogenous leukemia (AML) in non leukemic patients, 2) in association with myelodysplastic disorders with leukemic transformation or chroic myelogenous leukemia (CML) with impending blastic crisis, and 3) in association with known AML[1].

There have been many reports about the treatment of granulcytic sarcoma with combination chemotherapy, which has shown a similiar response as leukemia[1,9,14~19]. Radiotherapy has been widely used for treatment of symptomatic, tumorous and infiltrative leukemic lesion. Radiotherapy was given for palliative aim to the granulocytic sarcoma with granulocytic leukemia. Also, combined radiotherapy and chemotherapy has been considered the optimal treatment of primary granulocytic sarcoma without leukemia[17].

We retrospectively analyzed 14 lesions of granulocytic sarcoma in 9 patients at the Department of Radiation Oncology, Yonsei University College of Medicine, in an attempt to identify various clinical settings in which granulocytic sarcoma may occur; to review our experience with irradiation of granulocytic sarcoma; and to evaluate the treatment results for the radiation dose response. We hope that this data may provide some useful information which can be applied in the management of those patients with irradiation.

MATERIALS AND METHODS

1. Patients Characteristics

The 9 patients with granulocytic sarcoma treated from March 1987 to March 1992 were treated at the Department of Radiation Oncology, Yonsei University, College of Medicine. There were six males and three females. The age range was 6 to 57 years, and the median age was 30 years. In the 9 patients, 14 lesions of granulocytic sarcoma had

Table 1. Patient Characteritics of 9 Patients with Granulocytic Sarcoma

No.	Age/Sex	Sites	Dx. methods	Clinical settings	RTx. Energy	RTx. Total dose	RTx. response	Outcome
1	30/f	sternum	clinical	CML	6 MeV	2000	PR	3mo lost
2	51/m	T6 spine	Bx.	CML	Co-60	2000	CR	1mo death
		pelvic b.	clinical		Co-60	3000	PR	
3	13/m	clavicle	Bx.	no leukemia	Co-60	2000	CR	11 mo
		forhead	clinical		6 MeV	1400	PR	death
		zygoma Rt.	clinical		9 MeV	1400	NR	with AML
		chin Lt.	clinical		Co-60	1400	NR	
4	33/m	scapula	Bx.	no leukemia	Co-60	5000	CR	15mo NED
		cervical LN	Bx		Co-60	3000	CR	
5	46/f	T12 spine	CT	CML	Co-60	2200	CR	2mo death
6	6/m	perianal skin	Bx.	AML	12 MeV	2500	PR	2mo death
7	19/m	T6. extradural soft tissue	myelogram	AML	Co-60	2400	CR	6mo death
8	57/f	T6-10 paravertebral soft tissue	MRI	CML	Co-60	2000	CR	6mo death
9	52/f	gingiva	clinical	AML	Co-60	2000	CR	4mo death

Abbreviations: Bx, Biopsy; CT, Computed Tomography; MRI, magnetic resonance imaging; AML, acute myeolcytic leukemia; CML, chronic myelocytic leukemia; CR, complete response; PR, partial response; NR, no response

developed. At presentation, 5 lesions of 4 patients had pathologic confirmation of granulocytic sarcoma by biopsy and the other 5 patients who had a prior diagnosis of granulocytic leukemia were diagnosed by clinical findings and imaging studies (CT, MRI, myelography). Three patients had acute myelocytic leukemia, 4 patients had chronic myelocytic leukemia or hypereosinophilic syndrome, and the other 2 patients had no evidence of leukemia. The locations of the lesions were variable. The bone was the most frequently involved site, followed by soft tissue, lymph nodes, and skin.

Fourteen lesions of 9 patients with granulocytic sarcoma were treated with local irradiation. All patients received combination chemotherapy with a regimen similiar to AML (Table 1).

2. Radiotherapy Methods

External irradiation was given with megavoltage irradiation, electron beam (6, 9, 12 MeV) on the superficial mass or Co-60 on the deep seated tumor. The irradiation field covered the tumor mass with a generous margin. The prescribed dose fraction in the majority of patients was 200 to 300 cGy, and ranged from 180 to 400 cGy, fraction 5X/week. The total dose ranged from 1400 to 5000 cGy, and the majority of patients were treated with the total dose greater than 2000 cGy (Table 1).

The response to irradiation was evaluated regarding to the criteria recommended by Chak, et al[17]. The responses were subjective with some patients also having findings which could be followed objectively. A complete response was defined as total disapperance of symptoms and signs during the follow-up period. A partial response was defined as clinically significant reduction in symptoms with a greater than 50% reduction in objective findings. Marginal improvement in symptoms or progression of disease was considered as no response.

Treatment response was evaluated according to the age distribution, the hematopathologic diagnosis, the involved lesion and the total dose of irradiation. The survival was counted from diagnosis of granulocytic sarcoma.

RESULTS

1. Response of Treatment

The response to irradiation was as follows; complete response rate was 57% (8/14): partial response rate, 29% (4/14): no response rate, 14% (2/14). The overall response rate (CR+PR) was 86%.

The complete response according to the age distribution was shown in one of the 5 lesions of the

2 patients who were younger than 14 years old and in seven of the 9 lesions of the 7 patients who were older than 14 years old. The response rate in patients older than 14 years was 100% and the response rate in patients younger than 14 years old was 60%.

By the clinical settings, the complete response was noted in two of 3 in AML, 3/5 in CML, 3/6 in patients without leukemia. The response rate of patients with leukemia was better than that of patients without leukemia (Table 2). Also, with respect to the involved lesion, complete response was 4/6 in bone, 2/5 in soft tissue, and 1/1 in lymph node. The response rate of bone (100%) was better than that of soft tissue (60%) (Table 3).

By grouping the treatment courses according to the total dose of irradiation, the 2 lesions treated with less than 2000 cGy had no response (2/3), compared to the 8 lesions treated with from 2000 to 3000 cGy, which all showed response (8/8). Also the lesions which were treated with greater than 3000 cGy showed a response in all cases (3/3). The response rate was as follows: less than 2000 cGy, 33%; 2000-3000 cGy, 100%; greater than 3000 cGy, 100% (Table 4) (Fig. 1). It appeared that the response rate of lesions treated with the total dose greater than 2000 cGy was better than the total dose less than 2000 cGy. The majority of lesions (10/14) was treated with Co-60 r-ray in which almost all cases showed complete response, the other 4 lesions were treated with a electron beam (6, 9, 12 MeV) in which the response was either partial (2/4) or no response (2/4).

Table 2. The response According to Clinical Settings in 14 Lesions

Clinical settings	No. of sites	Response			response rate (%)
		CR	PR	NR	
AML	3	2	1		3/3
CML	5	3	2		5/5
no leukemia	6	3	1	2	4/6 (67)

Table 3. The response According to Site of Involvement in 14 Lesions

Sites	No. of sites	Response			response rate (%)
		CR	PR	NR	
bone	6	4	2		6/6 (100)
soft tissue	5	2	1	2	3/5 (60)
lymph node	1	1			1/1
skin	1		1		1/1
others	1	1			1/1

Table 4. The response According to Total Radiation dose in 14 Lesions

Total dose (cGy)	No. of sites	Response			response rate (%)
		CR	PR	NR	
less than 2000	3		1	2	1/3 (33)
2000-3000	8	6	2		8/8 (100)
more than 3000	3	2	1		3/3 (100)

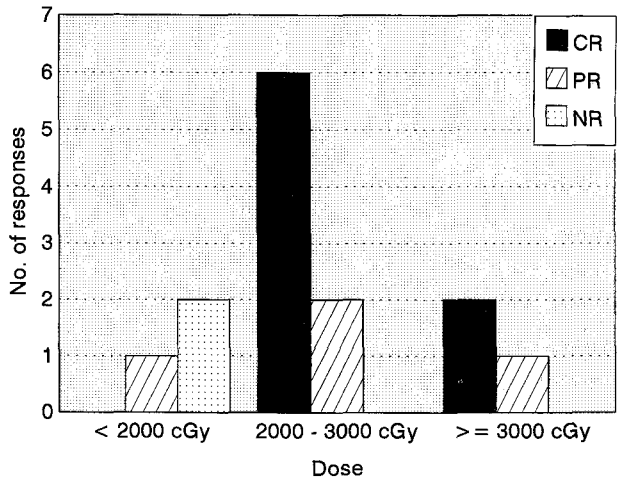

Fig. 1. The response by total radiation dose.

2. Survival

Follow up information was available in eight patients. The median survival was 5.6 months with range of 1 to 15 months. All except 1 patient died of leukemia or of complication from leukemia. The median survival of patients responding to radiotherapy was 4.9 months. Only one patient who was diagosed initially without leukemia, was treated by concomitant chemo-radiotherapy for curative intension, showed complete response and remained alive without development of leukemia at 15 months.

DISCUSSION

Granulocytic sarcoma is a localized tumor of immature myeloid cells. It is uncommon, occuring in 6.8% of patients with granulocytic leukemia at autopsy in one series[6] and caused clinical significant symptom in 2.9% of patients in another series[7].

Pathologic confirmation of granulocytic sarcoma should be done. The presence of eosinophilic myelocyte had been the evidence in the pathologist who had to diagnose granulocytic sarcoma before the development and use of the NASD (naphthol-ASD-chloroacetate esterase) stain in histologic section. However, the eosinophilic granulocyte was discovered only in 50% of lesions[9]. Some special stains can be very helpful in making and confirming the diagnosis of granulocytic sarcoma. The positive staining of the cytoplasm of tumor cells with NASD is practically unique to granulocyte and its precursors. This NASD stain was first described by Gcmori[11] in 1953 and later confirmed by Maloney et al[12] in 1960 and Leder at al[13] in 1970. Before the widespread use of this stain, diagnosis was extremely difficult and virtually impossible. In addition, immunoperoxidase staining with anti-lysozyme (muramidase) and ultrastructural intracytoplasmic dense granule by transmission electron microscopy could contribute to a definitive diagnosis of granulocytic sarcoma[1].

The periodic association of granulocytic sarcoma and acute myelocytic leukemia is extremely variable and the prognosis depends on the clinical context in which the tumor occurs. Granulocytic sarcoma occurs primarily in three clinical settings 1) as a forerunner of AML in nonleukemic patients, 2) as a sign of impending blastic crisis in CML or leukemic transformation in myelodysplastic disorders and 3) as a tissue manifestation in patients with established AML[1,8]. The most common clinical setting is for granulocytic sarcoma to develop in a child who either has, or is destined to develop, leukemia. Granulocytic sarcoma may precede the development of an acute leukemia by widely disparate time periods ranging from one to 49 months (mean 10.5 or 6 months)[1,9]. In the current series, only one in 3 patients initially without leukemia developed leukemia 11 months late. Although these tumors sometimes signalled relapse of disease, the appearance of granulocytic sarcoma dose not appear to worsen the already poor prognosis of accompanying AML. Granulocytic sarcoma in three AML patients of this study was developed with initial manifestation of AML. Eight patients had a prior history of CML (7 patients) and hypereosinophilic syndrome (1 patients). The development of granulocytic sarcoma in such patients during the indolent phase of myeloproliferative disorders appears to be a poor prognostic sign and is often followed by blastic crisis or leukemic transformation[1,10].

The clinical spectrum of granulocytic sarcoma is broad and virtually any site can be involved. The most commonly involved lesions in decreasing order of occurence are bone and periosteum, soft tissue overlying bone, lymph node, skin, and finally viscera[1,9,14]. Bone, soft tissue, and lymph node was the decreasing order in the current series. The single presentation was more common (8/14) than multiple presentation.

Although the radiosensitivity of leukemic cells in lymphocytic leukemia has been systematically studied and the results successfully applied to treat patients with this disease, the similiar studies of radiation response of granulocytic sarcoma in granulocytic leukemia are still lacking. Because these lesion are sensitive to irradiation as well as to chemotherapy, good response to the treatment of granulocytic sarcoma with radiotherapy has been reported sporadically[15~18]. The majority of patients are referred for pain palliation in the patients with granulocytic leukemia. In the present series, external beam radiotherapy with combination chemotherapy was completed in 14 lesions of 9 patients, and 8 lesions in 7 patients were referred for palliative aim.

There have been no studies reporting the correlation between the response to irradiation and the age distribution, the clinical settings or involved lesions. The patients older than 14 years old or with leukemia (AML or CML) or bone involvement

showed good response in this study. But this is not conclusive because the number of subjects was very small. The recommendation for dose of primary external beam therapy is 2000 to 3000 cGy for an 86% to 89% response rate[16,17]. The majority of our patients received irradiation of total dose a greater than 2000 cGy, and its response rate was 100% (11/11). But the response rate of lesions which received irradiation of a total dose of less than 2000 cGy was 33%. So this study demonstrated that a better response rate was noted with a total irradiation dose of 2000 to 3000 cGy. There were no correlations between their better response to radiotherapy and survival in patients with ganulocytic sarcoma.

There were no prospective studies on the treatment of primary granulocytic sarcoma but they would be expected to respond similiarly to other leukemias[1]. Longterm survivors without leukemia of primary granulocytic sarcoma treated with aggressive chemo-radiotherapy have been reported in various studies and case reports[9,18,19]. It has been suggested that not all granulocytic sarcoma inexorably leads to acute leukemia. Meis et al[9] reported that seven of 16 patients wih primary granulocytic sarcoma did not develop leukemia. All were treated with an intensive chemotherapy protocol utilized in leukemia patients with additional local irradiation at the involved site. In this study, only one patient initially without leukemia treated by combined chemo-radiotherapy regarding to curative intension showed complete response and remained alive without development of leukemia at 15 months. It is still uncertain whether or not this patient may develop acute leukemia.

Based on our experience with the present study and the review of literature, we recommend that all granulocytic sarcoma should be treated with aggressive chemotherapy and radiotherapy, especially in the patients without leukemia, where chemotherapy is similiar to the cases of AML and radiotherapy is local field irradiation with above 2000 cGy of total dose, which would show excellent results for curative or palliative aim.

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= 국문초록 =

Granulocytic Sarcoma : 방사선 치료 성적

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1987년 3월부터 1992년 3월까지 연세의료원 암쎈터 치료방사선과에서 방사선치료를 받은 Granulocytic sarcoma 환자를 대상으로 이들의 치료성적과 방사선 선량반응 관계를 알아보기 위해 후향성 분석을 하였다.

14예의 Granulocytic sarcoma 병변이 9예의 환자에서 발생하였고 급성, 만성 골수구성 백혈병 또는 무백혈병 상태 등과 같은 다양한 임상적 시기에 발생하였다. 병소 부위는 내림 순으로 골, 임파절, 연부 조직과 피부이었다. 모든 14예의 병변은 외부 방사선(Co-60 또는 전자선)으로 치료 받았고 대다수의 병변이 2000 cGy 이상의 전 방사선 선량으로 국소 방사선 치료를 받았다. 연령 분포와 발생한 임상시기는 치료에 대한 반응과 관련이 없는 것으로 나타났다. 골에서 발생한 임상시기는 치료에 대한 반응과 관련이 없는 것으로 나타났다. 골에서 발생한 병변은 다른 부위에서 발생한 병변에 비해 치료에 대한 반응이 더 좋은 것 같았다. 2000 cGy 이상의 방사선 선량을 받은 병변은 100% (11/11)의 월등한 국소 제어율을 보였지만 2000 cGy 이하의 방사선 선량을 받은 병변은 33% (1/3)의 감소된 국소 제어율을 보였다.

결론적으로 국소 방사선 치료는 Granulocytic sarcoma의 완화 또는 완치 목적의 치료에 있어 효과적이며 이때 2000 cGy 이상의 방사선 선량이 필요한 것으로 생각된다.