Radiation Therapy in the Treatment of HIV-related Kaposi's Sarcoma

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Abstract. *Background: Kaposi's sarcoma (KS) is the most frequent neoplasm occurring in patients with HIV-related AIDS and very often exhibits multifocal distribution so that a systemic approach is needed. KS is considered a radiosensitive tumor and (RT) has always played an important role in the therapeutic strategy of its various forms. RT is a valuable means of pain relief, bleeding control and edema palliation, but it is also an effective treatment modality for local control of skin and mucosal lesions in KS. The purpose of the present article is to report the results obtained by the Radiotherapy Unit of S. Camillo-Forlanini Hospital in Rome in the management of 38 AIDS-associated KS lesions and to assess the efficacy of RT in the treatment and local control of KS. Patients and Methods: Eighteen patients histologically-diagnosed with HIV-related KS underwent RT in the period between January 2002 and January 2012 at the Radiotherapy Unit of S. Camillo-Forlanini Hospital in Rome. In all cases, the lesions caused pain or discomfort and a thorough careful clinical evaluation had indicated a radiation treatment. A total of 38 lesions were treated with radiotherapy. Fifteen patients received systemic chemotherapy. Eight patients with multiple cutaneous lesions on their legs and arms were treated with a radiation schedule prescribing extended cutaneous irradiation using 6 -18 MeV electron beam energy, 200 cGy per fraction and a total dose between 24-30 Gy, according to the depth of lesions. One of these patients had also a cutaneous lesion on an eyelid that was treated with a radiation schedule using 6 MeV electron beam energy and bolus of 1 cm, 200 cGy per fraction and a total dose of 30 Gy. Seven patients with single cutaneous lesions on the legs and arms were treated using a photon regimen of 6 Mv energy, 200 cGy per fraction and a total dose between 20 and 36 Gy. Two patients had oral mucosa lesions and they were treated with a radiation schedule prescribing irradiation using 6 Mev photon regimen and personal mask, 200 cGy per fraction and a total dose of 24 and 30 Gy, respectively. A patient with a single bone lesion on the spinal column was treated with irradiation using 6 Mev photon regimen, 300 cGy per fraction and a total dose of 30 Gy. Results: At the time of reporting, 14 patients were alive and four patients had died. One patient died due to complications from HIV infection. The follow-up from the end of the treatment ranged from four to 124 months (mean=51.17 months). The overall survival for the group was 88.8% at one year. The mean overall survival was 57.4 months. A complete response was achieved for 31 lesions (83.8 %); a partial response with a tumor regression was observed for six lesions (16.2 %). No relapses were observed during the period of follow-up, but we observed new lesions in one patient. According to the Radiation Therapy Oncology Group scale we observed erythematic and dry desquamation (grade 1) in eight sites (21%); in only one patient (2.6%) did stomatitis occur (grade 1). Good cosmetic results were described for 25 (65.7%) out of 31 lesions. Effective palliative action was obtained for all lesions except for two (5.2%) located in a vertebra and hard palate. Conclusion: RT will be a mainstay of cure for this group of patients especially when of young age and the will to preserve the cosmetic appearance is a primary need.*

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Since its discovery 150 years ago, four different variants of Kaposi's Sarcoma (KS) have been described. Classic or Mediterranean KS in 1872 (1), African or endemic KS, iatro-genic or post-transplantation KS, and finally epidemic

or associated with acquired immunodeficiency syndrome (AIDS) in 1981 (2). Every type is related to human herpes virus-8 infection (3), whereas immunosuppression is a recognized risk factor only for post-transplantation and HIV-related forms (4). Epidemic KS incidence has diminished over time with the introduction of highly-active anti-retroviral therapy (HAART) (5). KS requires an individualized approach to treatment based on the extent, location, presence of tumor associated symptoms and patients' tolerance to treatment. Chemotherapy is essential for the treatment of widespread disease and visceral involvement, while local therapies such as radiotherapy (RT) may be adequate for localized disease.

KS is considered a radiosensitive tumor (6,7) and RT has always played an important role in the therapeutic strategy of the various forms, even if with different aims and results. RT is a valuable means of pain relief, bleeding control and edema palliation, but it is an effective treatment modality for local control of skin and mucosal KS lesions.

The purpose of the present article is to report on the results obtained by the Radiotherapy Unit of S. Camillo-Forlanini Hospital in Rome in the management of 38 AIDS-associated KS lesions and to assess the efficacy of RT in the treatment and local control of KS.

Patients and Methods

Eighteen patients histologically-diagnosed with HIV-related KS underwent RT in the period between January 2002 and January 2012 at the Radiotherapy Unit of S. Camillo-Forlanini Hospital in Rome. All patients were male, with a mean age of 43.5 years (range=28-58 years). After a clinical evaluation with regard to general medical condition, ECOG performance score 0 (55.5%), 1 (38.8%) and 2 (5.5%), the patients were studied by physical examination, full blood count, gastrointestinal endoscopy and computerized tomography (CT). The patients were classified according to the system of Mitsuyasu and Groopman (8) as KS stage I (fewer than 10 skin lesions for a single anatomic site) for eight cases (44.4%), stage II (more than 10 skin lesions or more than one anatomic site) in eight patients (44.4%) and stage IV (cutaneous and visceral lesions) in only two cases (11.1%), none was evaluated in regard to subtypes A and B (the presence or not of systemic signs or symptoms). All the patients were also staged according to the classification made in 1997 by the AIDS Clinical Trials Group Oncology Committee (9): T0 exclusive lesion of skin and/or lymph node in 12 patients (66.6%), T1 (non-lymph node visceral disease, oral involvement or tumor-associated edema or ulceration) for six cases (33.3%); I0 (CD4+ cell count > 200 cell/μl) four out of 11 patients (22.2%) and I1 (CD4+ cell count ≤200 cell/μl) for seven out of 11 cases (38.8%). As mentioned above, no other symptomatic illness evaluation was made (S0 and S1). In all cases, the lesions caused pain or discomfort and a thorough careful clinical evaluation had indicated a radiation treatment. A total of 38 lesions were treated with radiotherapy.

When first examined, 15 patients had receveid systemic chemotherapy. Liposomal doxorubicin (15 mg/mq) for at least six cycles over a four-month period was commonly administered. Out of 15 cases, we had four complete responses (CR) and eleven partial responses (PR). Taxol-based chemotherapy needed to be employed for only two patients as a salvage therapy after PR. HAART was received by every patient with a good viral load control of <50 copies of HIV RNA/ml in 12 cases.

Immunological conditions and the several clinical evaluation made us consider use of RT employment to palliate and reduce tumor burden.

Best RT treatment was customized for each patient in terms of energy, fractions and total dose in accordance to size, site, distribution and lesion depth. The most commonly treated areas were the left leg and left foot (11.1%) (Table I).

Eight patients with multiple cutaneous lesions on legs, arms were treated with a radiation schedule prescribing extended cutaneous irradiation using 6-18 MeV electron beam energy, 200 cGy per fraction and a total dose of between 24 and 30 Gy, according the lesion depth. One of these patients also had a cutaneous lesion on an eyelid that was treated with a radiation schedule using 6 MeV electron beam energy and bolus of 1 cm, 200 cGy per fraction and a total dose of 30 Gy. Seven patients with single cutaneous lesions on legs and arms were treated using a photon regimen of 6 Mev energy, 200 cGy per fraction and a total dose of between 20 and 36 Gy. Two patients had oral mucosa lesions and they were treated with a radiation schedule prescribing irradiation using 6 Mev photon regimen and personal mask, 200 cGy per fraction and a total dose of 24 and 30 Gy respectively. A patient with a single bone lesion on spinal column was treated with irradiation using 6 Mev photon regimen, 300 cGy per fraction and a total dose of 30 Gy.

At each review of follow-up, the irradiated lesion was evaluated in terms of objective and subjective responses to treatment. Tumor response was considered as complete (CR) in the case of clinical disappearance of the Kaposi's lesions, referring to the mass and not to the pigmentation of the lesions and a partial remission (PR) if there was at least a 50% reduction of the lesion; any reduction of less than 50% was considered as a non-response (NR). Acute and late treatment toxicities were recorded. Acute toxicity was defined as any toxicity that occurred within three months of the RT while late toxicity was defined as that which occurred after three months. Acute toxicity included skin erythema, dry desquamation, moist desquamation and necrosis or gangrene. Late toxicities included pigment change, telangiectasia, ulceration and edema. Skin tolerance was considered satisfactory if there was erythema (grade I reaction), moderate reaction (grade II), when there was dry epidermitis, severe reaction, with exudative epidermitis (grade III), and/or ulceration or necrosis (grade IV).

Results

At the time of reporting, 14 patients were alive and four patients had died. One patient died due to complications of HIV infection. The causes of death of the remaining three patients were not the result of complications of their HIV infection, nor a direct result of the KS lesions.

Follow-up from the end of the treatment ranged from between 4 to 124 months (mean=51.17 months). The overall survival for the group was 88.8 % at 1 year. The mean overall survival was 57.4 months.

A CR was achieved for 31 lesions (83.8%); a PR with tumor regression was observed for six lesions (16.2%). No

Table I. *Patients' characteristic*.

	Gender	Mean age, years	ECOG	Stage	RT	CHT	Site of disease
N=18	Male (n=18)	43.5 (range=28-58)	0, n=10 N=8	I	N=18	N=15	Left leg, left foot (11.1%)
	Female (n=0)		1, n=7	II N=8		N=4 CR	Right leg, left tigh, calf (8.3%)
			3, n=1	IV N=2		N=11 PR	Face, right groin, right thigh, right arm (5.5%)
							Hard palate, left arm, left hand, right foot (2.7%)

Table II. *Results of radiation therapy.*

	No. alive	No. died	Follow-up (mean range)	Mean overall survival	Complete response	Partial response	Relapse	New lesions
	N=14	N=4					0	1
Months			51.17	57.4				
Lesion, n					31	6		

relapses were observed during the period of follow-up but we observed new lesions in one patient (Table II).

The treatment was always well-tolerated, and there were no skin reactions of such severity requiring cessation of the radiotherapy. According to the RTOG scale, we observed erythematic and dry desquamation (grade 1) in eight sites (21%); in only one patient (2.6%) was stomatitis (grade 1) recorded.

Good cosmetic results were described for 25 lesions (65.7%) out of 31 CR. Effective palliative action was obtained for all lesions except for two (5.2%), located in a vertebra and hard palate.

Discussion

Kaposi's sarcoma is the most frequent neoplasm occurring in patients with HIV-related AIDS and very often exhibits multifocal distribution so that a systemic approach is needed. The management of AIDS-associated KS is evolving. The introduction of HAART in 1997 dramatically changed the prognosis for the specific disease. HAART can obtain a durable clinical response rate in over 60% of patients (10) and even in patients who do not have extensive disease, it is able to provide complete local resolution (11). Chemotherapy as a first-line approach can provide a response rate of 25%, with a median duration of four months (12, 13). Liposomal daunorubicin and doxorubicin are the standard-of-care while VP-16 and paclitaxel have become second or third-line drugs following use of liposomal agents. Some authors described a cumulative response rate when HAART is administered with pegylated liposomal doxorubicin than when it is used alone, with complete or partial response attained in ≥75% of patients (14,15). When HAART is able to reduce HIV RNA to undetectable levels, chemotherapy may no longer be required.

In the pre-antiretroviral therapy era the management of symptomatic lesions was largely attempted with palliative radiotherapy (16), as the prognosis was related to progression of the underlying HIV infection and immune suppression.

Nowadays, RT represents an effective treatment modality for local control for skin and mucosal lesions. There have been reports in the literature of high objective remission rates (93%) in the radiotherapeutic management of cutaneous KS. Responsiveness of the lesions is more than 90% (17) and CR occurs in 70% (18, 19). Cooper and Fried (20) reported on a subjective CR in 14 out of 26 treated sites, partial response in three sites and no response in four sites. Wit reported an objective response rate of 34% with subjective palliation in 90% of cases after using an 8-Gy single-fraction technique (21).

With this retrospective study of our experience in the treatment of this malignancy, we can recommend RT as

treatment for local control and palliation for pain and psychological discomfort for patients with cutaneous KS. According to the literature, our response rate (more than 90% including CR and PR) confirms the importance of RT in the management of local KS lesions. Greater doses (>20 Gy) are associated with a higher response rate, a lower incidence of residual pigmentation and a longer duration of tumor control (22,23), but these data suggest that doses should be tailored to the individual patient's needs. In fact, eyelid and conjunctival KS seems to be more radiosensitive than that in cutaneous sites: a high objective remission rate of 96% was observed at doses ranging from 10 to 20 Gy (24). Side effects are rare, and radiation is usually well-tolerated with minimal skin reactions. Another rather common affected site in patients with AIDS-related KS is the oral cavity. These lesions are usually associated with pain and swallowing disorders, requiring for efficient treatment. Irradiation of symptomatic oropharyngeal lesions has been problematic because these patients experience a high degree of radiation-induced mucositis even after low-dose irradiation therapy. Le Bourgeois reported the experience of 27 patients with mucosal KS receiving 15 Gy to the oral cavity; severe reactions were observed in six (22%), moderate reactions in four (15%) and mild reactions in 17 (63%) (24). They recommended the use of prophylactic anti-fungal treatment in oropharyngeal irradiation in order to reduce toxicity. In our study, we included two patients with oral lesions; we observed a good response in terms of regression of KS and palliative action and only a moderate toxicity as stomatitis.

Recurrences in non-involved adjacent skin depend greatly on the progression of the underlying AIDS, hence multiple local fields of irradiation are given during evolution of disease for the same patient. In our study, we observed only one recurrence with a new lesion on an arm in a patient who was been treated on the face.

Palliation of symptomatic visceral or mucosal disease should nearly always be attempted first by chemotherapy and modern HAART. However, there are rare instances in which a patient's lesion fails to respond to systemic chemotherapy. These patients may benefit from attenuated doses of local irradiation to control skin KS or to palliate bleeding and pain.

Conclusion

Long-term survival continues to improve in patients with HIV and the incidence of cancers is increasing in the aging population. HAART and chemotherapy are indicated by current guidelines, while the best treatment options need to be customized for single patients by physicians experienced in treating patients with HIV disease. RT will be a mainstay of cure for this group of patients especially due to their young age and when the will to preserve the cosmetic appearance is a primary need. Future studies need to address the role of RT in the anti-retroviral era and specifically for patients with extensive disease.

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