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Special Article

Systemic Cytotoxic Therapy of Basal Cell Carcinoma

A Review of the Literature

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Abstract—*Fifty-five cases of systemic, cytotoxic therapy of patients with basal cell carcinoma have been reported in 53 patients in the English literature since the first report in 1960. Cytotoxic therapy without cis-platinum was used in 28 cases, resulting in only one partial response. On the contrary, 17 out of 22 evaluable patients (77%) responded to systemic treatment with cis-platinum-containing regimens. In 10 patients (45%) complete disappearance of the tumor was noted. These patients survived for a median time of more than 22 months (range 4+ to 51+ months). Although the experience is limited, the use of cis-platinum-containing regimens seems justified in the rare instances of metastatic disease, or when local treatment fails. When the primary tumor is very large, pretreatment with cis-platinum alone or in combination might be of value.*

INTRODUCTION

BASAL CELL CARCINOMAS (BCC) of the skin, the most common form of human cancer, grow slowly and almost always present as local tumors [1]. Local therapies such as surgery and/or radiotherapy lead to cure rates above 95%, both modalities being equally effective [1, 2]. However, these tumors may occasionally behave more aggressively. Despite adequate primary therapy, they recur locally and produce large, destructive lesions. Moreover, a small number of tumors will metastasize to regional lymph nodes or to bone, lung, and liver [2, 3]. It is estimated that hundreds of patients in the U.S.A. die annually or become disfigured [4].

The experience with systemic cytotoxic therapy (CT) in the treatment of BCC is limited. In general, these tumors are regarded as relatively insensitive to CT [1, 5].

Cytotoxic therapy of a patient with locally, recurrent basal cell carcinoma (BCC) where CT resulted in complete disappearance of the tumor [6] provoked a survey of the literature. In the present paper, we report a review of the literature concerning 53 patients treated with CT for BCC.

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MATERIALS AND METHODS

After failure of surgery and radiotherapy in the treatment of a patient with BCC, a recurrent BCC in the right orbital region was treated with systemic CT as a last resort. The lesion disappeared completely, and the result was described in a case report [6].

Out of curiosity we looked for relevant references by database searching (Medlars) in collaboration with the University Library using the following keywords: BCC, drug therapy. Many cases of locally administered CT, especially 5-fluorouracil, were reported. However, no reports on systemic CT were found. We therefore performed a manual search in the *Index Medicus* from 1983 to 1989, and we found five reports dealing with systemic CT of BCC. By means of the reference lists in these reports, we were able to trace other reports. In this way another 25 studies were collected.

Including our own patient we evaluated the therapeutic efficacy of CT in BCC in terms of response and survival in a total 53 cases reported in the literature. If possible, response criteria according to WHO were applied [7]. Complete response (CR) is defined as disappearance of all known disease for at least 4 weeks. Partial response (PR) is defined as a decrease of 50% or more of the lesion(s) for at least 4 weeks, without progression of any tumor element and no occurrence of new elements. No

change (NC) is defined as disease with less than 50% decrease and less than 25% increase, and no new elements. Progressive disease (PD) is an increase of 25% or more or the appearance of a new lesion. If response evaluation was done according to WHO in the original report, this evaluation was used in Tables 1 and 2. Otherwise, a retrospective evaluation was tried by the authors of the present paper based upon the WHO criteria, if possible. Not evaluable (NE) is used in Tables 1 and 2, when retrospective analysis of the response was not possible. In all cases, the authors stated that BCC were histologically confirmed. Survival is defined as the time from start of treatment with chemotherapy until death or last control. Relative risks and frequencies expressed in percentages are followed by 95% confidence intervals.

Table 1. Systemic cytotoxic therapy for BCC using non-cis-platinum-containing regimens

Reference	No.	CT	RR*
Antimetabolites			
Van Scott, 1960	1	M	PR[2,4]
	5	M	NC
Chien, 1966	1	M	NC
Hall, 1970	1	F	NC
Costanza, 1974	1	F	NC-PR[2,3]
Mikhail, 1977	1	M	NC
Sakula, 1977	1	M	NC
Farmer, 1980	1	F	NC
Farmer, 1980	1	M	NC
Scanlon, 1980	1	M	PD
Alkylating agents			
Assor, 1967	1	N	NC
Hughes, 1973	1	N	NC
White, 1975	1	K	NC
Farmer, 1980	1	C	NC
Antibiotics			
Liu, 1971	1	T	NC
Mikhail, 1977	1	B	NC
Safai, 1977	1	B	NC-PR[3]
Wieman, 1983	1	B	NC
Combination chemotherapy			
Murphy, 1975	1	MC	NC
Curry, 1977	1	MC	NC
Jagar, 1977	1	VB	NC[3]
Briggs, 1979	1	CAF	NE[3]
Christensen, 1980	1	CAF	NC
Woods, 1980	1	MVB	NC-PD

Abbreviations: No. = number of patients; Surv. = survival; PRT = prior radiotherapy; CRT = concomitant radiotherapy; CT = cytotoxic therapy; P = *cis*-platinum; M = methotrexate; F = 5-fluorouracil; C = cyclofosfamide; A = Adriamycin®; B = bleomycin; V = vinblastine. RR = response obtained; CR = complete response; PR = partial response; NC = no change; PD = progressive disease; NE = not evaluable.

*1: Response according to WHO [7] was done in the initial report. 2: Response was done retrospectively by the authors of the present study. 3: Retrospective evaluation of response was not possible or difficult. 4: Response documented by photograph.

RESULTS

Since Van Scott *et al.* [8] reported the first case in 1960, 30 other reports were found in the English literature dealing with a total of 53 patients treated with systemic CT for either locally advanced or metastatic BCC. Two patients were treated with two different CT regimens. Twenty-two of the 31 studies are case reports and the remaining nine report small series of two to eight cases. Only two surveys were found [2, 9]. Phase II trials of cytotoxic therapy of BCC have never been done.

The median age of the 53 patients was 62 years (range 33–88 years). Median survival was 13+ months (range 2–51 months). In six patients, evaluation of response to CT was not possible. Eighteen out of the remaining 47 patients (38%, 25–53%) had objective response. Ten patients (21%, 11–35%) obtained complete response (CR) whereas PR was noted in eight patients (17%, 8–30%). In 30 cases an objective response was not seen.

Non-cis-*platinum-containing regimens*

Between 1960 and 1983 a number of different non-*cis*-platinum-containing chemotherapeutic modalities were used (Table 1). A total of 28 patients treated with non-*cis*-platinum-containing chemotherapy for BCC have been reported [2, 8–14].

Van Scott *et al.* [8] treated six patients with intravenous methotrexate alone. They noted 'some response' in most patients. In one patient they observed 'definite response', but according to the published photograph the reduction seems less than 50%. In another patient with multiple BCC in the face, a photograph documented reduction of some tumors and disappearance of others.

During the next 20 years, eight patients were treated with methotrexate either as single agent or as part of a combination therapy without obtaining any response. Costanza *et al.* [2] reported a possible objective response in 1974. After 2 months of treatment with 5-fluorouracil a large thigh ulcer healed completely, whereas moderate increase in pulmonary metastasis were seen. However, this could not be stated as PR according to WHO because specification of size was not done. Bleomycin was used as second-line treatment, inguinal lymph nodes decreased in size, but the pulmonary nodules remained unchanged.

In 1977 Jagar *et al.* [14] treated a 55-year-old man with a combination of vinblastine and bleomycin and obtained 'partial response'. The patient had infiltration of the bone marrow with pancytopenia. CT resulted in regression of cyto-

Table 2. Systemic cytotoxic therapy for BCC using cis*-platinum-containing regimens*

Reference	No.	RT	Age (years)	CT	RR*	Surv. (months)
Salem *et al.* [15]	2	—		P	CR[1]	1+
		—		P	PR[1]	7+
Woods and Stewart [12]	1	—	66	P C	PR[1]	12+
Guthrie and Porubsky [19]	3	PRT	68	P A	CR[1]	30+
		PRT	80	P A	CR[1]	31+
		PRT	88	P A	PR[1]	12
Wieman *et al.* [10]	1	—	58	P V	CR[2,4]	9+
Coker *et al.* [9]	1	PRT	63	P B	NC[2]	28+
Cieplinski [16]	1	—	58	P F B	PR[1,4]	39+
Robert *et al.* [21]	3			P B M	NE[3]	
				P B M	NE[3]	
				P B M	NE[3]	
Guthrie *et al.* [18]	5	—	58	P A	CR[1]	22
		PRT	60	P A	NC[1]	2+
		PRT	72	P A	PR[1]	3+
		—	71	P A	CR[1,4]	26+*
		—	85	P A	PR[1,4]	20*
Luxenberg and Guthrie [20]	6	—	64	P	CR[1]	10+
		—	71	P A	CR[1,4]	26+
		PRT	70	P A	CR[1]	51+
		—	70	P A	NC[1]	16+
		—	62	P A	PR[1,4]	11+
		—	85	P A	PR[1,4]	20
Hartmann *et al.* [17]	1	PRT	62	P	NC[2]	16
Robinson [4]	3	CRT	82	P A	NE[3]	18+
		CRT	72	P A	NE[3]	24+
		—	78	P A	NC[1]	12+
Chawla *et al.* [22]	1	—	56	P A C	CR[2,4]	30+
Pfeiffer *et al.* [6]	1	PRT	74	P F B	CR[1,4]	18+

Abbreviations: see Table 1.
*Patient was probably included in [20] too.

penia with normalization of peripheral blood smear for 8 months.

In the same year, Safai and Good [11] reported that bleomycin had induced a partial response. However, a concomitant squamous carcinoma was found at autopsy. In the rest of the patients (Table 1) no objective response was noticed.

Overall, in 28 patients receiving non-*cis*-platinum-containing CT only one patient had a definite PR (response rate 4%, 1–18%). In another two patients PR might have been induced. Median survival were 8 months (range 2–36 months).

Cis-platinum-containing regimens

Reports of 27 patients treated with *cis*-platinum-containing regimens have been published (Table 2). Two patients had prior treatment with CT. Median age was 70 years (range 58–88 years). The patients received a median number of three courses (range 2–12). Objective response was noted after a median of two CT courses (range 1–6).

During a phase I trial using continuous infusion of *cis*-platinum, Salem *et al.* [15] reported in 1978 that one patient obtained complete response (CR) lasting 4+ months and another obtained partial response (PR) lasting 7+ months.

Woods and Stewart [12] and Wieman *et al.* [10] used *cis*-platinum as second-line cytotoxic treatment, and obtained one CR and one PR.

Cieplinski [16] observed 'more than 50% decrease in size of lymph nodes, complete healing of scrotal lesions and marked regression of pulmonary nodules' using *cis*-platinum, bleomycin and 5-fluorouracil.

Hartman *et al.* [17] reported that '*cis*-platinum had resulted in stabilization of cervical vertebral metastases with mixed lytic and blastic change'. The lesions were previously treated with RT, so evaluation of response was not possible. Coker *et al.* [9] reported 'subjective relief' and that 'bone scan showed improvement of bone metastases'. According to WHO this cannot be stated as PR.

In these seven patients *cis*-platinum was used for metastatic disease. In the remaining 20 patients CT was given for locally advanced disease.

Guthrie *et al.* [18, 19] used *cis*-platinum 75 mg/m^2 and doxorubicin 50 mg/m^2 in eight patients. Two of these patients were probably included in the

report by Luxenberg and Guthrie [20]. Five patients had objective response and, of these, three patients had a complete response lasting 22 to 31+ months. Apparently, all patients had reduction of tumor size after one course of therapy.

In six patients with BCC of the periorbital region Luxenberg and Guthrie [20] noted CR in three patients, PR in two patients and NC in the last patient. Five patients were treated with *cis*-platinum and Adriamycin® and one patient, achieving CR, received *cis*-platinum alone. Responses were usually noted within the first month of treatment.

In a study of six patients with skin carcinoma, Robert *et al.* [21] treated three patients with BCC. The results were not specified for BCC, but in all three CR, one PR and two NC were obtained. The durations of responses were 5 to 19+ months.

Robinson [4] treated three patients with the same regimen as Guthrie *et al.* [18, 19] and Luxenberg and Guthrie [20]. One had a less than 50% reduction of tumor and in two other patients response was not stated after treatment with CT. The addition of RT resulted in one PR and one CR lasting more than 18 and 24 months, respectively.

Chawla *et al.* [22] used Adriamyin®, cyclophosphamide and intra-arterial *cis*-platinum in a patient with two localized BCCs. CR was obtained in both cases, however a small microscopic remnant was found in one of the lesions.

Pfeiffer *et al.* [6] chose a combination of *cis*-platinum, bleomycin and 5-fluorouracil in the treatment of a 74-year-old woman with recurrent basal cell carcinoma, formerly treated with RT. The tumor disappeared completely for 12 months.

In patients treated with *cis*-platinum containing regimens, 17 out of 22 evaluable patients (77%, 55–92%) had a documented objective response. Five patients were not evaluable, either because of concomitant RT or because response was not specified for BCC. Ten CR (45%, 25–67%) and seven PR (32%, 14–54%) were obtained. Five patients (23%, 8–45%) did not obtain objective response. Four patients received *cis*-platinum as single agent chemotherapy, two CR, one PR and one NC were obtained. When treated with *cis*-platinum in combination, response was recorded in 14 out of 18 patients. Median survival was 16+ months (range 3+ to 51+ months).

DISCUSSION

BCC is in general curable by surgery and RT [1]. However, local therapies may fail to cure some patients. Due to the large number of patients with BCC, recurrent and/or destructive lesions are not rare.

Metastatic BCC is rarely seen. Only 113 cases are reported in the English literature [5]. Patients with metastatic BCC have a grave prognosis, with median survival of 10–14 months from the time of metastases [9, 23]. In these cases chemotherapy may therefore be indicated.

Moreover, treatment of either initially or at recurrence large BCC (>5 cm) poses a difficult therapeutic problem [24]. Local control with RT is poor and surgery may result in functional and cosmetic impairment. Exploring combined treatment modalities in these advanced cases may be useful.

Even though BCC are malignant tumors of low grade, the reduction in tumor size is often seen during the first or second course of CT. Only rarely have long follow-up times been stated, since few patients have been followed for more than 2 years. The duration of response and/or survival are seldom stated because of early reporting.

Although the experience is limited, treatment with *cis*-platinum alone or in combination has led to a rather high rate of response, including CR in almost half of the published cases. In contrast, therapy with antimetabolites, alkylators and some antibiotics seems without major activity.

Although the patients in the literature represent a highly selected group, the results seem promising. *Cis*-platinum appears to be the most effective cytotoxic drug in BCC. It is not clear whether other cytotoxic drugs add to the effectiveness of *cis*-platinum or whether the duration of response may be prolonged by combination CT.

An increasing number of metastatic BCC are reported [3]. The reason for this is not clear but may result in a larger number of patients with BCC, who are candidates for chemotherapy with *cis*-platinum.

To verify the efficacy of *cis*-platinum in BCC, regular phase II or III trials are needed. However, collect the necessary number of patients in a single institution might be impossible. Until multicenter trials are established, it is therefore important that all cases of CT in BCC are reported. Ideally, reports must include evaluation of response according to WHO, documentation of response (photograph), duration of response, former and concomitant therapy, and survival.

In conclusion, regression of BCC can be achieved by treatment with *cis*-platinum. In metastatic disease or when local treatment fails, we suggest three to six courses of *cis*-platinum every 4 weeks and if an objective response cannot be established after 2 courses, treatment is discontinued.

When the initial or recurrent lesion exceeds 5 cm in diameter, RT rarely leads to local control [4]. Two or three courses of preoperative or preirradiation CT with *cis*-platinum may be considered in such cases.

REFERENCES

1. Haynes HA, Mead KW, Goldwyn RM. Cancers of the skin. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer. Principles and Practice of Oncology*, 2nd edn. JB Lippincott, 1985, 1343–1369.
2. Costanza ME, Dayal YT, Binder S, Nathanson L. Metastatic basal cell carcinoma: review, report of a case and chemotherapy. *Cancer* 1974, **34**, 230–235.
3. Scanlon EF, Volkmer DD, Oviedo MA, Khandekar JD, Victor TA. Metastatic basal cell carcinoma. *J Surg Oncol* 1980, **15**, 171–180.
4. Robinson JK. Use of combination chemotherapy and radiation therapy in the management of advanced basal cell carcinoma of the head and neck. *J Am Acad Dermatol* 1987, **17**, 770–774.
5. Kord JP, Cottel WI, Proper S. Metastatic basal cell carcinoma. *J Derm Surg Oncol* 1982, **8**, 604–608.
6. Pfeiffer P, Hansen SO, Rose C. Kemoterapi ved basalcellekarcinom. *Ugeskr f Læger* 1989, **151**, 2150–2151.
7. *WHO Handbook for Reporting Results of Cancer Treatments*. WHO offset publication No 48. Geneva, WHO, 1979.
8. Van Scott EJ, Shaw RK, Crounse RG, Condit PT. Effects of methotrexate on basal-cell carcinomas. *Arch Dermatol* 1960, **82**, 762–771.
9. Coker DD, Elias G, Viravathana T, McCrea E, Hafiz M. Chemotherapy for metastatic basal cell carcinoma. *Arch Dermatol* 1983, **119**, 44–50.
10. Wieman TJ, Shively EH, Woodcock TM. Responsiveness of metastatic basal-cell carcinoma to chemotherapy. A case report. *Cancer* 1983, **52**, 1583–1585.
11. Safai B, Good RA. Basal cell carcinoma with metastasis. *Arch Pathol Lab Med* 1977, **101**, 327–331.
12. Woods RL, Stewart JF. Metastatic basal cell carcinoma: report of a case responding to chemotherapy. *Postgrad Med J* 1980, **56**, 272–273.
13. Briggs RM, Pestana I. Long-term survival in basal cell carcinoma metastatic to bone: a case report. *Ann Plast Surg* 1979, **3**, 549–554.
14. Jagar RM, Weiner LJ, Howell RS. Basal cell carcinoma with bony metastases producing myelofibrosis. *Arch Dermatol* 1977, **113**, 1288–1289.
15. Salem P, Hall SW, Benjamin RS, Murphy WK, Wharton JT, Bodey GP. Clinical phase I–II study of *cis*-dichloro-diammineplatinum(II) given by continuous i.v. infusion. *Cancer Treat Rep* 1978, **62**, 1553–1555.
16. Cieplinski W. Combination chemotherapy for the treatment of metastatic basal cell carcinoma of the scrotum. A case report. *Clin Oncol* 1984, **10**, 267–272.
17. Hartman R, Hartman S, Green N. Long-term survival following bony metastases from basal cell carcinoma. *Arch Dermatol* 1986, **122**, 912–914.
18. Guthrie TH, McElveen LJ, Porubsky ES, Harmon JD. Cisplatin and doxorubicin. An effective chemotherapy combination in the treatment of advanced basal cell and squamous carcinoma of the skin. *Cancer* 1985, **55**, 1629–1632.
19. Guthrie TH, Porubsky ES. Successful chemotherapy of advanced squamous and basal cell carcinoma of the skin with *cis*-diaminedichloroplatinum II and doxorubicin. *Laryngoscope* 1982, **92**, 1298–1299.
20. Luxenberg MN, Guthrie TH Jr. Chemotherapy of basal cell and squamous cell carcinoma of the eyelids and periorbital tissues. *Ophthalmology* 1986, **93**, 504–510.
21. Robert NJ, Govil J, Clark J, O'Connor T, Wagner H, Ervin T. Combination chemotherapy for skin carcinoma. *Proc ASCO* 1985, **4**, C-538.
22. Chawla SP, Benjamin RS, Ayala AG *et al.* Advanced basal cell carcinoma and successful treatment with chemotherapy. *J Surg Oncol* 1989, **40**, 68–72.
23. Farmer ER, Helwig EB. Metastatic basal cell carcinoma: a clinopathological study of 17 cases. *Cancer* 1980, **46**, 748–757.
24. Fischbach AJ, Sause WT, Plenk HP. Radiation therapy for skin cancer. *West J Med* 1980, **133**, 379–382.