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Aclarubicin in Advanced Thyroid Cancer: a Phase II Study

HELLMUT SAMONIGG,* DIETER K. HOSSFELD,† JÜRGEN SPEHN,† HEIKO FILL‡ and GEORG LEB*

**Department of Internal Medicine, Karl-Franzens-University at Graz, Auenbruggerplatz 15, A-8036 Graz, Austria, †Department of Internal Medicine, University of Hamburg, Martinistraße 52, D-2000 Hamburg 20, F.R.G. and ‡Department of Nuclear Medicine, University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria*

Abstract—*Twenty-four patients with metastatic thyroid cancer were treated with aclarubicin intravenously at a dose of* 25–30 mg/m^2 *daily for* 4 *days and treatment was repeated every* 3 *weeks. None of the patients had previously received chemotherapy. Twenty-three patients received two or more treatment cycles and were evaluated for their response. One complete remission and four partial remissions were noted (objective remission rate* 22%*). Mean survival time was* 57 *weeks. Side-effects were evaluated in* 24 *patients with* 18 *patients receiving prophylactic antiemetic therapy. Nausea was observed in* 18 (75%) *and vomiting occurred in three patients* (13%). *In* 15 *patients* (63%) *there was mild myelosuppression. We conclude that aclarubicin alone represents an effective therapy in patients with metastatic thyroid cancer and that side-effects are minor.*

INTRODUCTION

APART from surgery, therapy for thyroid cancer includes radio-iodine and in some cases external radiation, along with the administration of a high dose of thyroid hormones. It is currently thought that the indication for cytostatic therapy is only given after exhausting these treatment modalities and in the face of progression of the disease [1–3].

Among other agents doxorubicin, cisplatin and bleomycin have been found as most effective agents for the therapy of thyroid cancer [4–8]. Most of the available reports are on doxorubicin monotherapy where remission rates of up to 30% are found for tumors of different histological types [9]. A limiting factor for the use of this cytostatic agent is its cardiotoxicity particularly when a cumulative dose of 550 mg/m^2 has been exceeded [10, 11].

Aclarubicin is an anthracycline derivative which exhibited distinctly lower cardiotoxicity in both preclinical and clinical studies [12]. Aclarubicin appears to be as effective as doxorubicin in the treatment of such malignancies as acute myeloid leukemia [13, 14]. Therefore we investigated the efficacy of aclarubicin used as single agent in a phase II study of metastatic thyroid cancer.

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Address for correspondence and reprint requests: Hellmut Samonigg, M.D., Department of Internal Medicine, Karl-Franzens-University, Auenbruggerplatz 15, A-8036 Graz, Austria.

MATERIALS AND METHODS

Twenty-four patients suffering from metastatic thyroid cancer underwent cytostatic treatment in three university medical centers between August 1981 and October 1986. Eleven patients had follicular cancer, five patients had medullary thyroid cancer and eight patients had anaplastic cancer. Eleven males and 13 females, age 19–74 (median 58 years) were studied. Before therapy the Karnofsky index [15] was higher than 60% in each patient. Twenty-one patients had previously received radio-iodine therapy and four had also received external radiation therapy of the tumor. Two patients with anaplastic cancer and one with medullary thyroid cancer had not received radio-iodine therapy or external radiation therapy. None of the patients had previously received cytostatic treatment. With the exception of two patients who had refused operation, primary therapy in all cases had been surgical removal of tumor. At the start of chemotherapy, all patients showed definite signs of disease progression. In the university medical centers of Graz and Innsbruck, patients received 25 mg/m^2 aclarubicin intravenously for 4 days. In the university medical center of Hamburg 30 mg/m^2 was given intravenously for 4 days. This 4-day therapy was repeated every 3 weeks in each patient. Patients received up to 15 treatment cycles with a median of five. The highest cumulative dose was 1353 mg/m^2. Eighteen patients received anti-emetics prophy-

Table 1. Patient data and response

Patient No.	Sex	Age at beginning of therapy (years)	Histology of tumor	Localization of metastases	Pretreatment*	Months of disease before chemo therapy	Karnofsky index at beginning of therapy	Aclarubicin dose (mg/m²/day for 4 days)	Cycles of therapy	Response (see text for abbreviations)	Time to disease progression (weeks)	Further therapy	Survival (weeks)
1	F	61	Anaplastic	Liver Skeleton	OP, RJ RT	156	80	25	6	NC	48	Chemotherapy (FU)	84
2	F	72	Follicular	Lung Liver	OP, RJ	6	90	25	7	PR	18	Radio-iodine	76
3	M	70	Follicular	Lung	OP, RJ	147	80	25	14	PR	38	Radio-iodine	140+
4	M	33	Anaplastic	Local	OP, RJ	6	90	25	15	MR	73	Palliative surgery	248+
5	M	70	Anaplastic	Liver Lung Local	OP, RJ	12	60	25	5	NC	12	None	20
6	F	53	Medullary	Lung	OP, RJ	7	60	25	4	MR	12	None	20
7	M	70	Follicular	Skeleton Lung Local	OP, RJ RT	7	70	25	5	NC	36	None†	68+
8	M	19	Medullary	Lung	OP, RJ	34	90	25	6	NC	40	None†	48+
9	F	68	Anaplastic	Skeleton Local	OP, RJ RT	107	70	25	4	NC	28	None	52+
10	M	57	Follicular	Lung Skeleton	OP, RJ	11	60	25	3	PD	—	None	14
11	F	54	Follicular	Lung	OP, RJ	54	100	25	5	MR	18+	—	18+
12	F	73	Follicular	Lung	OP, RJ	22	70	25	3	PD	—	None	36
13	F	49	Follicular	Local	OP, RJ	4	100	25	4	CR	15+	—	15+
14	M	74	Anaplastic	Local	OP, RJ	2	60	25	3	PD	—	None	16
15	F	47	Follicular	Lung	OP, RJ	6	70	25	2	PD	—	None	28
16	M	66	Anaplastic	Skeleton Lung	OP, RJ	40	60	30	1‡	—	—	None	—
17	F	62	Follicular	Skeleton Lung Liver	OP, RJ	46	60	30	2	PD	—	None	10
18	F	63	Follicular	Lung Skeleton	OP, RJ	22	80	30	7	NC	44+	—	44+
19	F	25	Medullary	Lung	OP, RJ	8	100	30	6	NC	42	None	84+
20	M	52	Medullary	Liver Skeleton	OP	2	60	30	2	PD	—	None	22
21	M	57	Anaplastic	Lung	None§	1	70	30	4	NC	15	None	48
22	F	58	Anaplastic	Lung Local	None§	1	90	30	5	PR	18	Chemotherapy (MTX, FU‖)	60
23	M	69	Medullary	Local	OP, PR	37	70	30	8	PR	32	None	68
24	F	66	Follicular	Skeleton	OP, RJ	47	70	30	2	PD	—	None	28

*OP: Operation; RJ: radio-iodine therapy; RT: radiotherapy; — data not available; FU: 5-fluorouracil; MTX: methotrexate.
†Patient refused further treatment.
‡Patient was lost to follow up, response not evaluable.
‖Followed again by partial remission.
§Patient refused surgery.

lactically (metoclopramide 10–30 mg daily for 4 days).

Patients were analyzed for response if they had received at least two treatment cycles. Thus, one patient was excluded (Patient 14, see Table 1). The following classification and criteria were used to assess remission: (CR) complete response, (PR) partial response, (MR) minor response, (NC) no change and (PD) progressive disease. CR was defined as complete disappearance of all tumor manifestations for at least 4 weeks. PR and MR indicated reduction of tumor mass by at least 50 and 25%, respectively. NC was defined as stationary behavior, i.e. a reduction of less than 25% and more

of tumor mass and/or the appearance of new tumor manifestations. PD denoted an increase of more than 25% of tumor mass.

RESULTS

Efficacy

Five of 23 patients (22%) achieved remission (1 CR, 4 PR). Taking into account the three patients with minor responses (MR), a tumor decrease was registered in 35% of all cases and in a further 35% stabilization took place. For the five patients who had achieved a remission (CR, PR) the mean survival time was 72 weeks. When the three patients with MR are included mean survival was 81 weeks. For those who did not respond to therapy mean survival was 40 weeks. The median time interval to disease progression was 24 weeks for responders (CR + PR) and 28 weeks when patients with MR were included. For the NC patients time to disease progression was between 12 and 48 weeks. Patient data and response are shown in Table 1.

Of the 11 patients with follicular thyroid cancer, one patient achieved a complete remission, two patients a partial remission and in one patient tumor size decreased by 25–50% (PR). The course of the illness stabilized in two patients (NC) and in the remaining five patients a definite progression was noted. Of the five cases of medullary thyroid cancer, one case of partial remission and one case of a reduction of tumor substance of 25–50% was recorded. Two patients showed no change of the disease and in one patient progression was noted. Of the seven patients with anaplastic thyroid cancer, one patient obtained a partial remission and one a minor response. In four patients stabilization of the progressive illness was seen (NC) and in one patient there was progression of disease (PD).

In this study, the slightly different doses of aclarubicin (25 mg/m^2/days 1–4, 15 patients and 30 mg/m^2/days 1–4, eight patients) had no detectable influence on the remission rate, the median survival time or the median time to disease progression.

Side-effects

Side-effects were recorded according to WHO criteria [16]. Apart from nausea and vomiting and leukopenia, side-effects were rarely noted (Table 2). The dose limiting factor was leukopenia. Thus, in four of the nine patients receiving 30 mg/m^2/days 1–4, a dose reduction of 20% became necessary. The incidence of alopecia (one patient out of 24) was unexpectedly low for an agent of the anthracycline group. While three patients showed signs of phlebitis at the injection site, two paravasates did not progress to abscess formation or necrosis. A temporary increase in serum glutamic oxaloacetic transaminase levels was found in 13 patients. Five patients received seven or more treatment cycles and four patients received a cumulative dose of more than 800 mg/m^2. None of the patients showed any signs of heart failure during aclarubicin therapy. None of the six patients who had coronary heart disease before therapy showed any symptoms of deterioration. Four patients had temporary sinus tachycardia immediately after aclarubicin injection. Repeat echocardiographic examinations showed no signs of deterioration of ventricular shortening fraction.

DISCUSSION

Thyroid cancers are rare and account for only 1% of all malignant tumors [17]. Only a small percentage of patients suffering from advanced thyroid carcinoma are eligible for chemotherapy when all other possible treatment modalities have failed [2]. For this reason, only very few studies on cytostatic agents in thyroid cancer are available and the number of patients treated is low. An analysis of all reports on cytostatic therapy in thyroid carcinoma shows that a complete or partial remission or at least a standstill of tumor growth can be expected in 30–50% of patients treated. With this rather unsatisfactory remission rate, one must take into account that these patients have been treated by all other available forms of therapy and chemotherapy is the only choice left.

Although the response rates in follicular (27%), medullary (20%) and anaplastic carcinoma (14%) were somewhat different, the size of samples is too small to decide whether aclarubicin does or does not have similar activity in the three histological types of thyroid cancer studied.

The results of prior studies [4, 6, 7, 18] with other chemotherapeutic agents for thyroid cancer suggest that well-differentiated thyroid cancer (papillary, follicular, Hürthle cell) and medullary carcinoma may be more responsive than undifferentiated types (anaplastic). In a randomized trial of doxorubicin versus doxorubicin plus cisplatin Shimaoka *et al.* [7] treated 92 patients with advanced thyroid carcinoma. Eighty-four patients were evaluable and the overall response rate was 21%. The response rate in the group of medullary carcinomas was 30% (three of 10 patients), in the group of well-differentiated carcinomas 23% (eight of 35 patients) and in anaplastic carcinomas 18% (seven of 39 patients). The difference in response rate between the three cell types was statistically significant. Gottlieb and Hill [6] treated 43 patients with adriamycin. While all histologic types of thyroid carcinoma responded, medullary (50% or three of six patients) and well-differentiated carcinomas (32% or seven of 22 patients) showed the best response. The response rate for anaplastic thyroid carcinomas (28% or four of 14 patients) was the lowest. Benker *et al.* [4] reported similar results after treatment with doxorubicin and bleomycin in 21 patients: three of

Table 2. Side-effects (number of patients)

WHO grade	0	1	2	3	4	No information
Nausea/vomiting	6	7	5	5	1	0
Infection	22	1	1	0	0	0
Leucopenia	9	3	8	3	1	0
Thrombopenia	22	1	1	0	0	0
Elevated SGOT	10	10	3	0	0	1
Elevated SGPT	13	6	1	1	0	3
Elevated serum Alkaline phosphatase	14	10	0	0	0	0
Alopecia	23	1	0	0	0	0
Diarrhoea	19	2*	1†	1*	0	1
Bleeding	23	0	1	0	0	0

*Chronic diarrhea due to medullary carcinoma of thyroid.
†Chronic diarrhea of unknown etiology, worse on days of therapy.

three patients with medullary carcinoma and three of eight with well-differentiated carcinomas responded to treatment, but only one of 10 with anaplastic carcinoma responded. In this study we found that all patients with bone metastases (eight out of 23) did not respond to chemotherapy. This observation is in agreement with the results of chemotherapy in other neoplasms than thyroid cancers that are highly insensitive to chemotherapy.

The results of our study reveal a success rate that is similar to that which has been reported (20–50%); however, side-effects were less severe. As far as the low incidence of vomiting and nausea is concerned this may be partly due to the fact that prophylactic anti-emetic therapy was given in 18 out of 24 patients. In spite of cumulative doses of up to 1353 mg/m^2, cardiomyopathy did not develop. This lends further support to the notion [12] that the use of aclarubicin, even in high cumulative doses, leads to a lower cardiotoxicity than doxorubicin, the most commonly used cytostatic agent for thyroid cancer.

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