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Original article

Experience in treatment of metastatic pulmonary carcinoid tumors

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Summary

Background: The only cure for patients with pulmonary carcinoids is surgery. In the present paper, we report the results of medical treatment of patients with metastatic tumors, their circulating hormone markers, and immunohistochemical profile of the tumors.

Patients and methods/Results: The response to systemic antitumoral treatment was studied in 31 patients with metastatic pulmonary carcinoids. Median survival from treatment start was 25 months. Alpha-interferon treatment has resulted in stable disease in 4 of 27 patients (median duration 15 months), while 23 patients showed progressive disease. Somatostatin analogues given as single drug treatment resulted in progressive disease. Streptozotocin and 5-fluorouracil resulted in progressive disease in seven of seven patients. Stable disease was obtained for 8 and 10 months respectively in two of two patients treated with streptozotocin + doxorubicin. Two of eight patients treated with cisplatinum + etoposide showed a significant decrease in tumor size lasting six and eight months respectively, and one displayed stable disease for seven months. Elevation of plasma chromogranin A was seen in 93%.

Conclusions: The results of systemic antitumoral treatment of pulmonary carcinoids with distant metastases are generally discouraging. Chemotherapy with cisplatinum + etoposide, or doxorubicin combined with streptozotocin or paclitaxel may be of value. Alpha-interferon and octreotide offer efficient symptomatic relief, but stabilizes tumor growth in merely 15% of the cases. Plasma chromogranin A is the most frequently elevated tumor marker.

Key words: alpha-interferon, chemotherapy, octreotide, pulmonary carcinoids

Introduction

Between 5% and 70% of the patients with pulmonary carcinoids will develop metastases [1–4], most often to regional lymph nodes but also distantly to the liver, bones, brain, subcutaneous tissue, or mammary glands. Metastases may occur late, years or decades after the initial diagnosis. The overall five-year survival rate is 87%–93% and the 10-year survival rate is 77%–87% [5–7]. The only curative treatment is surgery in order to remove the primary tumor and affected lymph nodes. Radiotherapy is primarily used as palliative treatment of local or bone metastases but may also be considered for the primary tumor area if radical surgery is not possible. Various regimens of chemotherapy have been tried, including combinations of cisplatinum + etoposide or streptozotocin + 5-fluorouracil (5-FU). Alpha-interferon has also been used on these patients. For symptomatic relief of disabling carcinoid syndrome, octreotide is useful, alone or in combination with α-interferon.

The indications for and effect of the various treatment regimens have so far not been sufficiently evaluated. Our first-line treatment in patients with metastatic pulmonary carcinoids has been α-interferon. In case of disabling carcinoid syndrome, α-interferon has been combined with octreotide. When this therapeutic regimen has failed, we have switched to streptozotocin + 5-fluorouracil (5-FU). Patients that showed progressive disease while using the latter combination have been converted to cisplatinum + etoposide as a third line therapy. Liver embolization with gel-foam has been used as second or third line treatment when the vast majority of the tumor burden was located in the liver. Our intention has been to monitor the patients every third month by means of CT scans or ultrasonography, and measurement of circulating tumor marker levels. In this paper, we report our experience of treating 31 patients with pulmonary carcinoid tumors, all harboring metastatic disease. We also describe the usefulness of measurements of various secreted peptides and amines as markers for diagnosis.

Patients and methods

Patients

The patient characteristics are summarized in Table 1. All patients with metastatic pulmonary carcinoids (n = 31; 14 men and 17 women) treated at the Department of Endocrine Oncology, University hospital, Uppsala were included in this study. Their median age was 60 years (range 15–84). Four patients had atypical carcinoids, while 27 patients

had typical carcinoids according to the recent WHO classification [8, 9]. The primary tumor was centrally located in 19 patients and peripheral in six patients; in the remaining six patients, the position of the primary tumor was not known. Surgery of the primary tumor had been performed in 22 patients according to the following: local excision in three (two of these were later subjected to repeated surgery with lobectomy and pneumonectomy, respectively), lobectomy in nine, bilobectomy in five (one of these was operated on during the study) and pneumonectomy in five cases. In addition, seven patients were operated on for distant metastases (brain, skin, mammary gland and ovaries two patients each, pituitary one patient) and one patient was subjected to repeated laser surgery for intrabronchial recurrences. Radiotherapy against the primary tumor or intrathoracic recurrence was given to seven patients, while seven received palliative radiotherapy for bone metastases, two for brain metastases and one patient for a pituitary metastasis. All patients had distant metastases and were in stage IV at the start of treatment except two patients (nos. 12 and 28) who were classified as stage IIIa because lymph node metastases were found at surgery of the primary tumor. Patient 12 was later reclassified as stage IV because of development of distant metastases and patient 28 was reclassified as stage IIIb because of extensive intrathoracic tumor growth. Metastases most frequently occurred to the liver (25 patients), bones (18 patients) and lymph nodes (12 patients), while four tumors metastasized to the brain and three to the mammary glands (Table 1); all except one patient (no. 28) had extrathoracic involvement. Carcinoid syndrome was observed in 16 patients (all harboring liver metastases), while two had ectopic Cushing's syndrome due to production of ACTH. Median follow-up time from treatment start was 25 months (range 4–106).

Hormones

Plasma chromogranin A, chromogranin B, serum pancreatic polypeptide (PP), serum calcitonin and serum human chorionic gonadotrophin subunits α and β (hCGα and hCGβ) were repeatedly analysed according to methods described earlier [10–14]. Urinary excretion of 5-hydroxy-indole-acetic acid (5'HIAA) was measured on two consecutive days and the mean value was calculated. Twenty-four hour urinary excretion of tele-methylimidazoleacetic acid (MeImAA), the principal metabolite of histamine, was measured as described earlier [15].

Treatment schedules

The various used treatments given to the individual patients is shown in Table 2. α-Interferon has been used in 28 patients and γ-interferon in 14. The dose of α-interferon has varied between 9–42 (median 15)

Table 1. Patient characteristics.

Patient	Sex	Age (years)	Follow-up (months)	Metastases	Stage	Position (primary tumor)
1	F	60	Alive, 69	Lymph nodes, liver	IV	Central
2a	F	51	†, 10	Liver, bones	IV	Central
3	M	64	†, 15	Liver, bones	IV	Central
4	M	70	†, 18	Liver, bones	IV	Periferal
5	F	62	†, 60	Lymph nodes, bones, ovary	IV	Periferal
6	M	68	†, 20	Lymph nodes, bones, pancreas	IV	Not known
7	F	36	Alive, 23	Liver, lungs, trachea, mammary gland	IV	Central
8a	F	35	†, 33	Lymph nodes, liver, bones, brain, subcutis, ovary	IV	Central
9	M	84	†, 81	Liver	IV	Central
10	F	76	†, 27	Liver, bones, lungs	IV	Periferal
11	M	63	†, 57	Liver, bones, adrenals	IV	Central
12a	F	60	†, 45	Lymph nodes, liver, bones	IIIa–IV	Central
13	M	55	Alive, 19	Lymph nodes, liver	IV	Central
14	F	38	†, 23	Lymph nodes, liver, bones	IV	Not known
15	M	75	†, 4	Liver	IV	Central
16	M	57	†, 41	Liver, pituitary	IV	Not known
17	F	72	†, 20	Liver, bones, subcutis	IV	Central
18	F	56	Alive, 40	Liver, bones	IV	Central
19a	M	45	†, 16	Lymph nodes, bones	IV	Central
20	F	67	†, 25	Liver, bones	IV	Central
21	F	65	†, 15	Liver, bones	IV	Periferal
22	F	45	†, 56	Liver, brain, mammary gland	IV	Central
23	M	75	†, 31	Liver, bones	IV	Central
24	M	52	†, 14	Liver	IV	Periferal
25	M	66	†, 20	Lymph nodes, bones, brain	IV	Central
26	M	57	†, 81	Liver	IV	Not known
27	F	44	Alive, 21	Mammary gland, ovary	IV	Central
28	F	71	Alive, 71	Lymph nodes	IIIa–IIIb	Central
29	F	74	†, 49	Lymph nodes, liver, brain	IV	Periferal
30	M	15	Alive, 18	Lymph nodes, liver, bones	IV	Not known
31	F	39	†, 106	Liver	IV	Not known

Abbreviations: a – atypical carcinoid; † – dead.
Patients 12 and 28 had no detectable metastases at the inclusion. They are classified as stage IIIa because lymph node metastases were found at surgery. Patient 12 later developed distant metastases and was thus reclassified as stage IV, and patient 28 developed advanced intrathoracic disease and was thus reclassified as stage IIIb. Follow-up time is recorded from treatment start.

Table 2 Treatments given to the patients. First line treatment in **bold**, second line treatment underlined, third line treatment in *italics*.

Patient	Surgery	Radiotherapy	Treatment
1		Primary tumor	**α-IFN+SMS**, (+γ-IFN), Str+5-FU
2	Pneumonectomy	Bones	**Lan**, α-IFN+SMS
3	Lobectomy		**α-IFN+SMS**, Cis+Et, *^{111}Octr*
4			**α-IFN+SMS**
5	Bilobectomy; ovary	Bones	**α-IFN**, α-IFN+γ-IFN
6	Lobectomy	Intrathoracic recurrence	**Cis+Et**, α-IFN, (+γ-IFN)
7	Bilobectomy; laser		**α-IFN+SMS**
8	Pneumonectomy; skin	Primary tumor	**α-IFN+SMS**, Str+5-FU, *Cis+Et*, Tax+Dox, Tax
9	Segmentectomy		**SMS**, γ-IFN+SMS
10	Lobectomy	Bones	**α-IFN**, γ-IFN
11		Bones	**α-IFN+SMS**, (+γ-IFN), Str+5-FU, *Cis+Et*, Emb, ^{111}Octr
12	Enucleation, pneumonectomy	Intrathoracic recurrence, bones	**α-IFN**, Str+5-FU, *Emb*, α-IFN+γ-IFN
13	Pneumonectomy		**Str+5-FU**
14			**Cis+Et+α-IFN**, Tax, *Strp+Dox*
15	Lobectomy		**α-IFN**
16	Lobectomy; pituitary	Pituitary	**α-IFN**, α-IFN+SMS, *α-IFN+γ-IFN+SMS*
17	Enucleation, lobectomy; skin		**α-IFN**, α-IFN+5-FU, *α-IFN+γ-IFN+SMS*
18	Pneumonectomy		**Tax+Dox**, α-IFN+SMS, *Emb*
19		Primary tumor	**Cis+Et**, α-IFN
20	Bilobectomy		**α-IFN+5-FU**, (γ-IFN), α-IFN+SMS
21		Bones	**α-IFN+γ-IFN**
22	Bilobectomy, brain, breast	Brain	**α-IFN+SMS**, Emb
23	Lobectomy		**γ-IFN+SMS**
24			**α-IFN+SMS**, Cis+Et, *MIBG*, SMS
25	Brain	Primary tumor, bones	**Cis+Et**, α-IFN+SMS
26	Lobectomy		**α-IFN**
27	Pneumonectomy; breast, ovary		**α-IFN**, Str+5-FU
28	Bilobectomy	Intrathoracic recurrence	**α-IFN**
29	Lobectomy	Brain	**α-IFN**, γ-IFN
30			**α-IFN+SMS**
31	Lobectomy		**Str+5-FU**, α-IFN, *Strp+Dox*, SMS, Emb, α-IFN+γ-IFN+SMS

Abbreviations: † – dead; α-IFN – α-interferon, γ-IFN – γ-interferon, SMS – octreotide; Lan – lanreotide; Cis – cisplatinum; Et – etoposide, Str – streptozotocin; 5-FU – 5-fluorouracil; Dox – doxorubicin, Tax – paclitaxel; Emb – liver embolization with gel-foam; ^{111}Octr – ^{111}In-Octreotide, MIBG – ^{131}I-MIBG. ( ), γ-interferon discontinued within two months because of side effects.

million units/week divided into 3 or 5 subcutaneous injections, and side effects and compliance have been taken into consideration when deciding on dose alterations. Somatostatin analogues have been administered to 18 patients (lanreotide in one case and octreotide in all 18), alone or in combination with interferon or chemotherapy. Altogether 18 patients have received chemotherapy. The following regimens have been used (Table 3): Cisplatinum + etoposide (n = 8), streptozotocin + 5-FU (n = 7), streptozotocin + doxorubicin (n = 2), α-interferon + 5-FU (n = 2), paclitaxel (n = 2) and paclitaxel + doxorubicin (n = 2). Liver embolization with gel-foam was performed in altogether five patients, on one occasion in one patient, on two occasions in two and on three occasions in two patients. Targeted radiotherapy was administered to three patients, two of whom received ^{111}In-Octreotide and one ^{131}I-MIBG

When evaluating the treatment outcomes, a $\geqslant$ 50% decrease of at least one hormone marker was considered a biochemical response, while a $\geqslant$ 25% increase of at least one hormone marker was considered biochemical progression Similarly, a $\geqslant$ 50% decrease in tumor size (product of two perpendicular measures on CT scan) was considered an objective response and a $\geqslant$ 25% increase in tumor size or the occurrence of new metastases was considered progression. Time to progression was defined as the time from treatment start to the first occcasion when progression was observed. Duration of response was defined as time from treatment start to the last occasion when disease was considered stable.

Table 3. Chemotherapy regimens used

Drugs, doses	Interval
Cisplatinum 45 mg/m^2 day 2–3 + etoposide 100 mg/m^2 day 1–3	4 weeks
Streptozotocin 2000 mg day 1 + 5-FU 400 mg/m^2 day 1	3 weeks
Streptozotocin 2000 mg day 1 + doxorubicin 40 mg/m^2 day 1	3 weeks
Paclitaxel 150 mg/m^2 day 1 + doxorubicin 40 mg/m^2 day 1	3 weeks
Paclitaxel 175 mg/m^2 day 1	3 weeks
α-Interferon 9–25 million units/week + 5-FU 500 mg/m^2 day 1–3	4 weeks

Immunohistochemistry

Analysis of the immunohistochemical profile of the tumor was performed wherever paraffin blocks could be collected (n = 18), according to methods described earlier The following antibodies were used: Ki-67, CD44, hCGα, GRP, serotonin, bcl-2, nm23 and p53 [16].

Table 4. Tumor markers and endocrine symptoms in patients with metastatic pulmonary carcinoids. Figures indicate the marker level divided by the upper reference limit

Patient	Endocrine symptoms	U-5'HIAA	U-MeImAA	CgA	CgB	PP	hCGα	hCGβ	ACTH	U-cortisol	Calcitonin
1[L]		⩽1	⩽1	⩽1	1.8	543	⩽1	⩽1	⩽1	⩽1	⩽1
2[L]	Diarrhea	4.0	⩽1	54	NA	⩽1	1.1	⩽1	⩽1	⩽1	⩽1
3[L]	Diarrhea	16	⩽1	30	5.3	⩽1	83	⩽1	⩽1	⩽1	⩽1
4[L]	Flush, diarrhea	1.6	1.3	147	2.6	⩽1	10	⩽1	⩽1	⩽1	⩽1
5		1.3	⩽1	2.3	NA	1.3	⩽1	⩽1	⩽1	⩽1	⩽1
6		⩽1	⩽1	5.1	NA	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1
7[L]		1.1	NA	4.1	1.5	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1
8[L]	Cushing	1.4	⩽1	3.5	1.5	⩽1	⩽1	⩽1	2.0	21	NA
9[L]	Flush, diarrhea	18	NA	57	NA	8.4	67	⩽1	⩽1	⩽1	⩽1
10[L]	Diarrhea	1.5	NA	12	NA	⩽1	⩽1	⩽1	NA	NA	NA
11[L]	Flush, diarrhea	8.8	1.9	34	5.1	⩽1	6.0	⩽1	⩽1	⩽1	⩽1
12[L]		⩽1	⩽1	8.2	1.2	⩽1	3.3	⩽1	⩽1	⩽1	⩽1
13[L]		1.4	NA	15	1.6	⩽1	13	⩽1	⩽1	⩽1	NA
14[L]	Diarrhea, cushing	12	1.3	70	1.1	⩽1	17	1.4	107	151	⩽1
15[L]	Flush	6.6	NA	NA	NA	⩽1	243	⩽1	NA	NA	⩽1
16[L]	Flush, diarrhea	9.3	NA	42	NA	⩽1	130	⩽1	NA	NA	⩽1
17[L]		2.2	2.1	102	NA	⩽1	9.2	⩽1	⩽1	⩽1	⩽1
18[L]	Flush, diarrhea	2.9	⩽1	51	3.9	⩽1	9.3	⩽1	⩽1	⩽1	⩽1
19		⩽1	⩽1	1.7	1.1	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1
20[L]	Flush	3.8	1.5	249	NA	12	15	⩽1	⩽1	⩽1	⩽1
21[L]		⩽1	⩽1	2.6	NA	⩽1	⩽1	⩽1	⩽1	⩽1	1.2
22[L]	Diarrhea	2.3	⩽1	2.2	NA	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1
23[L]	Flush	17	1.3	220	NA	6.2	55	⩽1	⩽1	⩽1	⩽1
24[L]	Flush, diarrhea	28	⩽1	1275	NA	⩽1	17	⩽1	⩽1	⩽1	NA
25		⩽1	⩽1	2.2	NA	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1
26[L]	Flush, diarrhea	1.2	NA	97	NA	2.3	1.2	⩽1	NA	NA	⩽1
27		⩽1	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1	NA
28		⩽1	⩽1	1.7	⩽1	⩽1	⩽1	⩽1	⩽1	⩽1	NA
29[L]		⩽1	NA	1.6	NA	2.0	⩽1	⩽1	⩽1	⩽1	⩽1
30[L]		⩽1	NA	12	3	NA	NA	NA	NA	NA	NA
31[L]	Flush, diarrhea	2.3	NA	149	NA	6.3	14	⩽1	NA	NA	⩽1
Number elevated/analyzed		21/31	6/21	28/30	12/14	8/30	17/30	1/30	2/25	2/25	1/24
% elevated		68%	29%	93%	86%	27%	57%	3%	8%	8%	4%

Abbreviations: 5'HIAA – 5-hydroxy-indoleacetic acid, MeImAA – tele-methylimidazoleacetic acid; CgA – chromogranin A; CgB – chromogranin B; PP – pancreatic polypeptide; hCGα – human chorionic gonadotropin subunit α; hCGβ – human chorionic gonadotropin subunit β; ⩽1, within reference range; NA – not analysed; [L] – liver metastases.

Statistics

Intergroup comparisons were made by the Mann–Whitney U-test. Correlations were analyzed by the chi-square test. $P < 0.05$ was considered significant. The Kaplan–Meier product limit method was used for survival analysis.

Results

Tumor markers

The results from measurements of hormone levels are shown in Table 4. Chromogranin A and B were the most frequently elevated hormones, 93% and 86% respectively. The levels of chromogranin A (times upper reference limit) were significantly higher than the chromogranin B levels ($P < 0.01$). Sixty-eight percent (21 patients) had increased U-5'HIAA. Patients with liver metastases had higher chromogranin A levels than patients without liver metastases ($P < 0.01$). A carcinoid syndrome was present in 16 of the 21 patients with elevated U-5'HIAA. The 16 patients displaying carcinoid syndrome had significantly higher U-5'HIAA levels than those five patients with elevation of U-5'HIAA but without the carcinoid syndrome ($P < 0.01$).

Biotherapy

Results of biotherapy in individual patients are shown in Table 5. Twenty-seven patients were treated with α-interferon, alone or in combination with octreotide and/or γ-interferon. Symptomatic relief of the carcinoid syndrome was obtained in 7 of 16 patients. Two patients had no detectable tumor disease and normal hormone levels at the start of adjuvant α-interferon treatment. They both developed metastases after 23 and 33 months respectively. In 21 of 27 patients (10 receiving only α-interferon, 10 treated with α-interferon + octreotide and one given α-interferon + γ-interferon), the tumor disease progressed radiologically ($n = 17$), biochemically ($n = 8$)

Table 5. Biotherapy (each treatment regimen) in individual patients with pulmonary carcinoids. Figures denote response duration (in the patients showing regression/stable disease) or time to progression (in those patients who progressed), expressed in months.

Patient	Treatment	Reponse			
		Biochemistry		Radiology	
1	α-IFN+SMS	Progression	2	Progression	2
2	Lan	Progression	2	Stable	2
2	α-IFN+SMS	Progression	3	Progression	3
3	α-IFN+SMS	Progression	2	Progression	2
4	α-IFN+SMS	Progression	4	Stable	11
5	α-IFN	Stable	27	Progression	9
5	α-IFN+γ-IFN	Stable	18	Regress	11
6	α-IFN	Stable	3	Progression	3
7	α-IFN+SMS	Stable	11	stable	11
8	α-IFN+SMS	Stable	6	Progression	3
9	SMS	Regress	13	Progression	7
9	γ-IFN+SMS	Stable	27	Stable	29
10	α-IFN	Stable	8	Progression	3
10	γ-IFN	Progression	2	Stable	2
11	α-IFN+SMS	Progression	6	Progression	8
12	α-IFN	Progression	23	Progression (metastases)	23
12	α-IFN+γ-IFN	Progression	2	Stable	2
15	α-IFN	Progression	3	NE	
16	α-IFN (+SMS)[a]	Stable	16	Stable	18
16	α-IFN+γ-IFN+SMS	Progression	1	stable	9
17	α-IFN[b]	Progression	6	Progression	6
17	α-IFN+γ-IFN+SMS	progression	2	progression	2
18	α-IFN+SMS	Stable	3	Progression	3
19	α-IFN	Stable	2	Progression	2
20	α-IFN+SMS	Progression	3	Progression	3
21	α-IFN+γ-IFN	Stable	4	Progression	4
22	α-IFN+SMS	Progression	2	Progression	6
23	γ-IFN+SMS	Stable	13	Stable	10
24D	α-IFN+SMS	Stable	4	stable	4
24	SMS	Progression	5	Progression	5
25	α-IFN+SMS	Stable	10	Stable	10
26	α-IFN	Stable	29	Progression	5
27	α-IFN	Stable	7	Progression	5
28	α-IFN	Orogression	31	Progression (metastases)	31
29	α-IFN	Stable	17	Progression	14
29	γ-IFN	Progression	7	Progression	6
30	α-IFN+SMS	Regress	18	Stable	18
31D	α-IFN	Stable	3	Stable	3
31	SMS	Progression	3	Progression	5
31	α-IFN+γ-IFN+SMS	progression	1	progression	2

Abbreviations: IFN – interferon; SMS – octreotide; Lan – lanreotide; NE – not evaluated; **D** – treatment discontinued because of insufficient clinical effect

[a] SMS was added after 15 months

[b] Octreotide was added after one year. Patients 1, 6, 11 and 20 stopped γ-interferon after less than two months because of side effecs.

and/or displayed intractable endocrine symptoms ($n = 2$). Four (4 of 27) patients, all harboring typical carcinoids, (three treated with α-interferon + octreotide and one with α-interferon as a single drug) showed stable disease for 15 months (median). There was no difference in the frequency of response among patients with or without the carcinoid syndrome, and no correlation could be detected between response to treatment and the results of any of the immunohistochemical analyses. There was no difference in objective response or survival between those patients treated with the combination of α-interferon + octreotide compared to α-interferon as single drug, neither did treatment response correlate to Ki-67 expression or any of the other tumor products analysed by immunohistochemistry.

The combination of α-interferon and γ-interferon was used in nine patients (of whom one had it as first line treatment). Three of these patients stopped γ-interferon after less than two months due to side effects. One patient, who had progressed on single treatment with α-interferon, was biochemically stable for 18 months and showed stable radiology lasting 11 months following inclusion of γ-interferon to the regimen. The other five patients progressed after 1–4 months. γ-Interferon was given as a single drug to three patients. In all three cases, γ-interferon was withdrawn within 1–6 months due to intolerable side effects (pt. no. 20) or progressive disease (pt. nos. 10 and 29). Two patients (nos. 9 and 23) received γ-interferon in combination with octreotide. Both were stable for 10 and 29 months, respectively. Progression was later recorded even in these cases.

Somatostatin analogues were given as single drugs in four cases resulting in progressive disease in all of them. One experienced disabling side effects, another patient benefited from relief of a carcinoid syndrome, but the remaining two had insufficient or short-lasting effects on their carcinoid syndrome.

Chemotherapy

Eight patients received 3–8 courses (median 6) of cisplatinum + etoposide. One patient was concomitantly given α-interferon (no. 14). The results are shown in Table 6. Two patients (both harboring typical carcinoids) had an objective response for six and eight months respectively, and one (with an atypical carcinoid) had stablilization of disease for seven months. The tumors in the remaining five patients (four typical carcinoids and one atypical) continued to grow after 3–4 months, although the hormones decreased and symptomatic relief was obtained in the patient who was treated with concomitant α-interferon. Patients with the carcinoid syndrome responded less frequently to cisplatinum + etoposide than patients without this syndrome ($P = 0.03$). There was no correlation between response to treatment and Ki-67 expression or any of the other tumor products analysed by immunohistochemistry.

Seven patients were given 5–15 courses (median eigth) of streptozotocin + 5-FU; two received concomitant α-interferon (Table 7). One patient showed stable disease for eight months and progressive disease after 12 months. The tumors of the other six patients were obviously resistant to streptozotocin + 5-FU and showed progression. Both patients treated with a combination of α-interferon and streptozotocin + 5-FU progressed.

Table 6 Results of the treatment with cisplatinum and etoposide.

Patient	Number of courses	Biochemical result	Response duration/ time to progression[a]	Objective result	Response duration/ time to progression[a]
3	4	Progression	2	Progression	3
6	6	Stable	6	Regress	6
8	4	Progression	2	Progression	3
11	7	Progression	8	Progression	4
14 (α)	6	Regress	6	Progression	4
19	6	Stable	6	Stable	7
24	3	Progression	3	Progression	3
25	8	Stable	8	Regress	8

γ – received concomitant α-interferon.
[a] In the patients displaying stable disease or regression the figures denote response duration and in those patients who progressed the figures show time to progression. Time is expressed in months.

Table 7. Results of the treatment with streptozotocin and 5-FU.

Patient	Number of courses	Biochemical result	Time to progression	Objective result	Time to progression
1	11	Progression	9	Progression	6
8 (α)	6	Progression	4	Progression	2
11 (α)	14	Progression	8	Progression	3
12	8	Progression	3	Progression	2
13	15	Progression	11[a]	progression	12[a]
27	6	Stable	5[b]	Progression	2
31	5	Progression	1	Progression	4

γ – concomitant α-interferon.
[a] This patient was biochemically stable for 9.1 and radiologically stable for 8.4 months.
[b] Response duration.
Time is expressed in months.

Streptozotocin + doxorubicin was given to two patients (11 and 12 courses respectively). Both patients (nos. 14 and 31, Table 2) displayed radiologically stable disease for 8 and 10 months, respectively. One of the patients showed decrease of hormone markers and the other one had biochemically stable disease.

The combination of paclitaxel + doxorubicin was used in two cases. One patient (no. 8) who received eight courses, was stable for nine months while the other (no. 18), being treated with 10 courses, had stable disease in the liver for 11 months although her bone metastases progressed after nine months.

Two patients were treated with paclitaxel as a single drug. One of them received three courses but showed progressive disease after one month. The other patient, who was subjected to eight courses altogether, displayed radiologically stable tumor size but progressed biochemically after seven months.

The two patients that were given 5-FU in combination with α-interferon both showed progressive disease after three and six months, respectively.

Targeted radiotherapy

Targeted radiotherapy was given as third or fourth line therapy in three patients. Two of these patients received ^{111}In-Octreotide and one was subjected to ^{131}I-MIBG. All three showed progressive disease at the first follow-up after 3–6 months.

Liver embolization

Five patients underwent liver embolization with gelfoam. The procedure was performed on one occasion in one patient, on two occasions in two patients and on three occasions in two patients. The patient that only had one embolization performed (no. 12) reported a temporary clinical improvement and the procedure resulted in biochemically stable disease for four months. Although the liver metastases decreased $< 50\%$, the disease progressed in other organs. After eight months, the liver metastases also started to grow and the hormone levels increased. One patient underwent embolization of both liver lobes with a two month interval (pt. no. 18). She was biochemically and radiologically stable until progression was noted 12 months from the first treatment. Another patient (no. 22) was embolized twice in the right liver lobe at four months' interval. Clinical improvement and biochemical and radiological regression were noted after the first procedure. Progressive disease was however noted 23 months after the first event. One patient underwent three embolizations of the right lobe at 1 and 1.5 years' interval, respectively (no. 31). Clinical improvement of disabling carcinoid

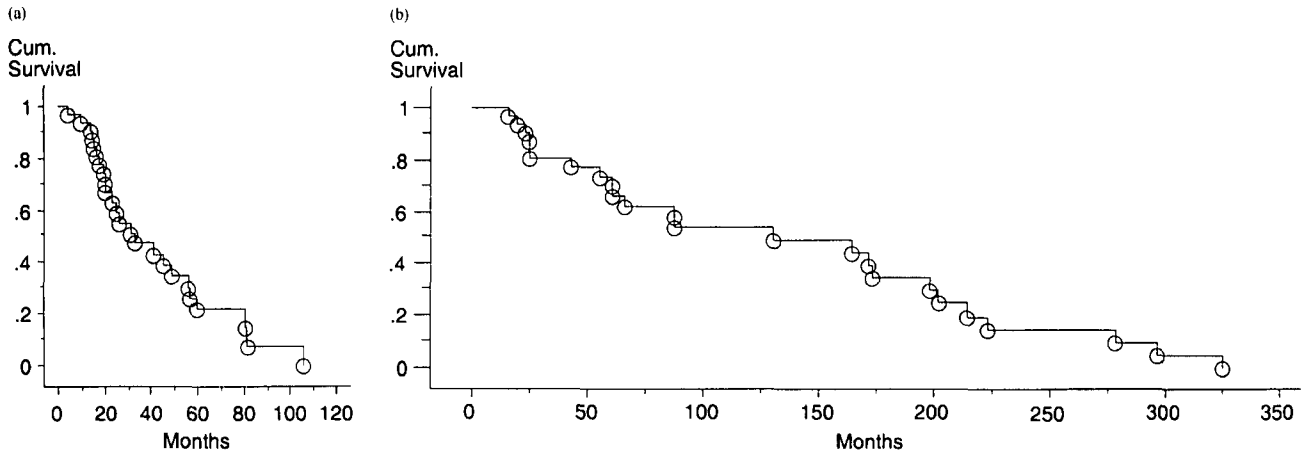

Figure 1. (a) Survival rate (Kaplan–Meier) from treatment start. (b) survival rate (Kaplan–Meier) from the initial diagnosis.

syndrome was observed after all three treatments. After the first embolization, she was radiologically stable for 11 months and the hormones decreased significantly. After the following two embolizations, she was biochemically stable but progressed radiologically. The last patient (no. 11) was first embolized in both lobes at two month intervals and after one year again in the right lobe. His hormones decreased after the first treatment and he was radiologically stable nine months after the first and 11 months after the third embolization.

Prognosis

Median survival from the initial diagnosis was 76 months (16–325). Five-year survival from treatment start was 22% (Figure 1a), while 5- and 10-year survival from the initial diagnosis was 70% and 54%, respectively (Figure 1b). Twenty-four patients have died after median 26 months (4–106), and seven patients are alive with disease after median 23 months (18–71).

Discussion

Plasma chromogranin A, which is recognized as a valuable tumor marker both in midgut carcinoids [17] and gastric carcinoids [18], appears to be the most sensitive marker in metastatic pulmonary carcinoids as well. Patients with liver metastases had higher chromogranin A levels than patients without liver metastases, which may imply a correlation between plasma chromogranin A level and tumor burden. The low specificity of a marginally increased chromogranin A level [19] makes it unreliable for differential diagnosis of a lung tumor found on chest X-ray. Only one patient with chromogranin A within the reference range had elevation of chromogranin B. The efficacy of chromogranin B as a marker for bronchial carcinoids has not been investigated, and the present data implies that a study designed for such an evaluation is warranted.

In our material of metastatic typical and atypical pulmonary carcinoids, the carcinoid syndrome occurred in half the patients. About two thirds had elevation of urinary 5'HIAA which may be used as a tumor marker in patients with metastatic pulmonary carcinoids. The elevation was however less prominent in the absence of carcinoid syndrome. None of the patients without Cushing's syndrome had elevation of plasma ACTH or urinary cortisol. In the absence of clinical symptoms, it does not seem useful to measure these two hormones.

For patients with malignant midgut carcinoids biotherapy with α-interferon and somatostatin analogues improves prognosis [20] and offers good symptomatic relief. In pulmonary carcinoid patients however, the effect of α-interferon and octreotide on tumor growth seems to be more limited; only a few patients showed stable tumor size. The benefit of adding γ-interferon to the α-interferon regimen is not very obvious in this patient material. Our study indicates that a substantial proportion of patients with pulmonary carcinoids suffering from the classical carcinoid syndrome are symptomatically relieved by α-interferon and octreotide.

Chemotherapy with streptozotocin and 5-FU has produced promising results in patients with endocrine pancreatic tumors [21], but the effect on pulmonary carcinoids is disappointing. On the other hand, consistent with earlier data in endocrine pancreatic tumors [22], some patients with pulmonary carcinoids may respond to streptozotocin and doxorubicin. The efficacy of treatment with the combination of doxorubicin and streptozotocin in patients with pulmonary carcinoids needs to be evaluated in a controlled study.

The rapidly growing SCLC are highly responsive to chemotherapy with cisplatinum and etoposide, although the response is usually short-lived. We have noted an objective response or stable disease in 3 of 8 patients with bronchial carcinoids. The patients showing significant reduction of tumor size had typical carcinoids with 1% and 3% Ki-67-positive cells, respectively. This is somewhat surprising considering the results of cisplatinum + etopside in treatment of endocrine pancreatic tumors, where functioning, highly differentiated tumors

did not respond. On the other hand, non-functioning, anaplastic tumors of the endocrine pancreas showed objective reduction in 67% of the patients [23]. Although none of the patients experienced complete remission and renal or neurologic side-effects limit the number of tolerated courses, this is still encouraging and should be further studied. Notably, all three patients responding to cisplatinum and etoposide with decrease or stable disease receceived this combination as first-line treatment for their carcinoids. On the contrary, only one of the five patients showing progressive disease received cisplatinum + etoposide as first-line therapy. If this means that cisplatinum combined with etoposide may be used as adjunctive treatment in cases when lymph node metastases are found at surgery of the primary tumor, the treatment still needs to be further studied in a randomized, controlled, multi-center trial, which will however have to wait until the anti-tumoral effect of the combination on pulmonary carcinoids has been confirmed.

The role of targeted radiotherapy in pulmonary carcinoids is still being investigated. None of our three patients treated with radiolabelled octreotide or MIBG benefitted from the therapy, but the limited number of patients and the fact that all three were suffering from advanced disease warrants caution when interpreting the data.

As could be expected from earlier data regarding midgut carcinoids [24], liver embolization may be of value for debulking of liver metastases even in patients with pulmonary carcinoids. We observed stable disease lasting more than one year, a decrease in tumor marker levels and symptomatic relief. The duration of the effect was however limited and most pronounced after the first embolization in each lobe.

The prognosis in our material of metastatic pulmonary carcinoids was poor. Although the five-year survival from initial diagnosis was 70%, five-year survival from treatment start was only 22%. This is due to the fact that these tumors may develop metastases late, after many years. Patients were usually not referred to us for medical treatment until distant metastases were recognized. It was not always possible to accurately determine how many of our patients had lymph metastases at primary surgery due to variable quality of the recording of the operative procedure. Since the risk to develop distant metastases is greater if lymph node metastases are present at diagnosis [5, 16, 25], a thorough dissection of peribronchial and hilar lymph nodes using frozen sections is mandatory during surgery for primary pulmonary carcinoids.

In conclusion, radical surgery still offers the only possibility to cure patients with pulmonary carcinoids. Although a few patients can survive for several years despite distant metastases, the treatment of patients with widespread disease is dismal. Liver embolization offers symptomatic relief and temporary stabilization. Individuals suffering from endocrine symptoms may benefit from the combination of α-interferon and octreotide. Chemotherapy, either with cisplatinum + etoposide or combinations containing doxorubicin may produce objective responses or stabilization of the disease for limited periods of time.

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