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The Role of Cytotoxic Chemotherapy in the Management of Aggressive and Malignant Pituitary Tumors

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ABSTRACT

Pituitary tumors are mostly benign lesions, although 5–35% are locally invasive. A small number exhibit a more aggressive course, infiltrating dura, bone and sinuses, and are designated highly aggressive. However, the presence of metastases separate from the pituitary in the central nervous system or at a distance is necessary to designate pituitary tumors as carcinomas, *i.e.* truly malignant. When conventional therapeutic modalities fail, systemic chemotherapy remains the last option. We report seven such patients, three with highly aggressive and four with malignant pituitary tumors (n = 4) four women; median age, 32 yr; range, 23–48 yr), who received one or more courses of chemotherapy with lomustine and 5-fluorouracil (median, two courses; range, one to six courses). Three patients with systemic metastatic disease had a shorter survival (median, 5 months; range, 1–14 months) than the one patient with central nervous system metastases alone (10 yr). A patient with an aggressive nonmetastatic prolactinoma who initially responded to chemotherapy died from another nondisease-associated cause. Two patients, one with an aggressive and one with a metastatic tumor, achieved symptomatic improvement with a median duration of 6 months. A hormonal reduction greater than 50% was observed in two of seven patients; only one patient who had an aggressive tumor obtained an objective tumor response. The median survival from the time of initiation of chemotherapy in patients with malignant tumors ranged from 3–65 months. Two patients with malignant tumors developed disease progression while receiving chemotherapy; no patient with extracranial metastases showed a response. Treatment was well tolerated, with minimal individual side-effects. Three patients with no response to initial treatment received different chemotherapeutic regimens with no additional response. All patients with metastatic malignant tumors eventually died.

Treatment with cytotoxic chemotherapy is noncurative, and current experience is limited. Until another more specific form of treatment is available, chemotherapy may still be of some value in patients with highly aggressive and malignant pituitary tumors, at least in achieving a temporary remission or delay in progression. The combination of lomustine/5-fluorouracil proved easy to administer with minimal toxicity, although the response rate was only 14%. Until a more specific treatment is found, an optimal chemotherapeutic regimen needs to be established. (*J Clin Endocrinol Metab* **83:** 4233–4238, 1998)

PITUITARY tumors are found in 10–20% of unselected autopsy and imaging series (1–3), whereas clinically overt tumors are found in only 0.02–0.025% of the population (4). Such tumors usually exhibit a benign course, but can occasionally become highly aggressive, infiltrating adjacent tissues and recurring repeatedly despite conventional treatment (5, 6). It is generally accepted that the presence within the central nervous system (CNS) of tumor tissue not contiguous with the pituitary fossa or other extracranial systemic metastases is needed to establish the diagnosis of a malignant pituitary tumor (carcinoma) (7–9). Using such criteria, the prevalence of pituitary carcinomas is thought to be around 0.1–0.2% of all cases of pituitary tumors (9, 10); almost all of these arise in tumors that were macroadenomas at presentation. However, as a number of pituitary tumors are only diagnosed as carcinomas at autopsy (7, 11), and more cases are being identified in recent years with the wider application of modern and more sensitive imaging modalities (12), this figure is probably an underestimate.

The conventional treatment of large pituitary tumors consists of surgery and, in some centers, conventional or focused radiotherapy; when appropriate, more specific treatment with dopamine agonists and/or somatostatin analogs may be useful. The combination of surgery and radiotherapy is usually effective in controlling the majority of such tumors (6, 9). However, tumors that are highly aggressive and recur repeatedly despite radical surgery and postoperative radiotherapy as well as frankly malignant tumors may require further treatment. The use of additional radiotherapy is limited by the risk of radiation necrosis to surrounding structures, although the role of stereotactic radiotherapy for well circumscribed tumors has not as yet been fully assessed. In most cases the outcome of such aggressive or metastatic tumors is poor, with visual loss, progressive neurological disability, and death (6).

There have been few studies of the results of combination cytotoxic chemotherapy in patients with pituitary carcinomas other than single case reports (13–15). Cytotoxic chemotherapy, although unlikely to be curative, might lead to clinically useful remission when the other therapeutic modalities have failed. We have reviewed our own experience using a specific chemotherapeutic regimen, the combination of 5-fluorouracil (5-FU) and cyclo-hexyl-chloroethyl-nitrosourea (lomustine, CCNU), as first line chemotherapy in patients with highly aggressive or malignant pituitary tumors. A number of patients who showed no response to the

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above treatment received other chemotherapeutic regimens. We have recorded the clinical, endocrine, radiological, and histopathological features of these tumors on presentation and at recurrence and on malignant transformation, and we have assessed the response rate to and outcome after chemotherapy.

Subjects and Methods

Patients and assessment

We have reviewed 7 patients with the diagnosis of highly aggressive pituitary tumors (n = 3) and pituitary carcinomas (n = 4) (4 women; median age, 32 yr; range, 23–48 yr) who received cytotoxic chemotherapy, referred to our department over a period of 27 yr (1970–1997). The patients with pituitary carcinomas, (patients 1–4; Tables 1 and 2) had systemic or CNS metastases. The diagnosis of highly aggressive pituitary tumors (patients 5–7, Tables 1 and 2) was based on the radiological and perioperative findings of extensive dural and surrounding tissue invasiveness and recurrence after surgery and radiotherapy. The clinical and endocrine features of 2 patients (no. 1 and 2) have been the subject of a previous report (15). Endocrine evaluation during the course of the disease was carried out using standardized basal and dynamic stimulation tests, as previously described (16). Six of the patients underwent transsphenoidal (n = 4) or transfrontal (n = 2) surgery at initial presentation, and all had further surgery during the course of the disease. The 3 patients with aggressive tumors had initial transsphenoidal surgery and later transfrontal surgery in an attempt to achieve local control of the tumor. All patients received external beam irradiation after surgical intervention. Pituitary irradiation was carried out using 4- to 15-MV linear accelerators to deliver a lesion dose of 4500 cGy (rad) in 25 fractions over 35 days. Treatment was planned individually using the smallest target volume compatible with uniform irradiation of the lesion as detected radiologically. With immobilization in an individually constructed, skin-tight, full-head plastic shell, with x-ray simulation and full isodosimetry, a dose-balanced 3-field technique (2 lateral and 1 frontal) was employed to localize radiation to the lesion and minimize the dose to the optic pathways, brain stem, and temporal lobes. Pituitary imaging was available before and after each course of chemotherapy in all patients and included contrast-enhanced computed tomography scans in 3 patients and gadolinium-enhanced magnetic resonance scans in 4 patients; 3 patients had both imaging modalities. These were reviewed by a single neuroradiologist and were used to assess disease response to treatment or progression. The initial histopathological findings and those from patients who were reoperated upon were evaluated by the same histopathologist. During each cycle of treatment with chemotherapy, the side-effect profile of the medication was also recorded. Response to treatment was defined in terms of symptomatic and/or secretory improvement (>50% reduction from the pretreatment value) and/or reduction in tumor size (>50% reduction of pretreatment size), according to WHO criteria. Adverse reactions to chemotherapy were recorded, specifically including gastrointestinal, neurological, and hematological side-effects. Three of the 4 patients who died as a consequence of their disease underwent an autopsy to establish the extent of malignant spread.

Chemotherapeutic regimens

The decision to initiate chemotherapy was based on deteriorating clinical and/or hormonal and/or radiological findings or the presence of CNS and/or systemic metastases. The chemotherapeutic regimen administered in the first instance (see below) is based on the responses of other neuroendocrine tumors to these drugs, as previously noted (17–19). A response to chemotherapy was recorded when there was either symptomatic improvement (a reduction in the symptoms of mass effects) and/or hormonal secretion reduction and/or radiological improvement. The development of new lesions while the patient was receiving chemotherapy was a reason to discontinue treatment. When no response or relapse after initial treatment occurred, a number of other therapeutic schemes were used (see below).

Standard regimen: day 1. On day 1, CCNU (100 mg/m^2) was given orally; folinic acid (350 mg) in 100 mL normal saline was given over 2 h, followed by 5-FU (400 mg/m^2) as an iv bolus, followed by 5-FU (400 mg/m^2) in 1 L normal saline over 22 h.

Standard regimen: day 2. On day 2, folinic acid (350 mg) in 100 mL normal saline was given over 2 h, then 5-FU (400 mg/m^2) was given as an iv bolus, followed by 5-FU (400 mg/m^2) iv in 1 L normal saline over 22 h.

The folinic acid/5-FU regimen was repeated at 3-week intervals; the CCNU dose was given at 6-week intervals. One cycle comprised one CCNU and two 48-h 5-FU/folinic acid infusions. All patients received the combination of CCNU/5-FU in the first instance, except patient 1 who had already received two courses of etoposide and *cis*-platin 3 yr previously. CCNU was administered to a total hematological tolerance level. Patients who did not respond to the above regimen and were considered sufficiently fit to tolerate more intensive therapy underwent further chemotherapy. Patient 3 received carboplatin alone (350 mg/m^2, iv) and in combination with α-interferon (3 megaunits, sc, three times per week). Patient 4 received carboplatin alone and in combination with CCNU/5-FU, and further treatment with dacarbazine (800 mg/m^2), whereas patient 1 received the combination of etoposide with *cis*-platin as the initial treatment.

Stereotactic multiarc radiotherapy (20), administered locally as a single treatment (1000 Gy), was given to patients 5, 6, and 7 with aggressive disease and to patient 4 with malignant disease.

Results

Clinical/endocrine/radiological details on presentation (Table 1)

Of approximately 2000 resected pituitary tumors included in our database, 4 patients had functioning pituitary carcinomas (patients 1–4; Tables 1 and 2), a prevalence of 0.2%; another 3 patients had highly aggressive tumors (patients 5–7; Tables 1 and 2). All patients with highly aggressive or malignant pituitary tumors had symptoms and/or signs associated with hormonal hypersecretion (2 with severe Cushing's syndrome and 1 with severe acromegaly) and/or tumor mass effects (headache or cranial nerve palsies). The severity

TABLE 1. Clinical, endocrine, and radiological features of metastatic malignant (carcinomas) or highly aggressive pituitary tumors at initial presentation, subsequently treated with chemotherapy

Patient no.	Diagnosis	Age (yr)	Tumor size, maximum diameter (mm)	Symptoms on presentation and secretory status
Carcinomas				
1	Prolactinoma (M)	32	Macroadenoma	Headache; PRL, 4060 mU/L
2	Prolactinoma (F)	48	Macroadenoma	Epilepsy associated with SIADH; PRL, 4200 mU/L
3	Prolactinoma (M)	23	Macroadenoma, 17 mm	Headache, visual failure in childhood; PRL, no initial value
4	Cushing's disease (M)	41	Macroadenoma, 18 mm	Cushing's syndrome; ACTH, 125 ng/L
Highly aggressive tumors				
5	Prolactinoma (F)	38	Macroadenoma	Cranial nerve palsies; PRL, no initial value
6	Acromegaly (F)	27	Macroadenoma, 14 mm	Clinical acromegaly; GH, 400 mU/L
7	Cushing's disease (F)	28	Macroadenoma, 12 mm	Clinical Cushing's syndrome; ACTH, 65 ng/L

SIADH, Syndrome of inappropriate (vasopressin) ADH secretion; (M), male; (F), female.

TABLE 2. Response to chemotherapy in patients with malignant (1–4) and highly aggressive (5–7) pituitary tumors

Patient no.	Chemotherapy	Extent of disease	Side effects	Response to chemotherapy	Outcome
(1) PRL mU/L	CCNU/5-FU × 2 cycles	Pituitary fossa Liver, Lungs	None	Cl: ? Improved but liver mets noted Hor: PRL ↓ from 550000 to 90000 mU/L Rad: No change CT pituitary	Died 4 weeks after liver mets noted and 3 months after initiation of chemotherapy
(2) PRL	CCNU/5-FU × 1	Pituitary fossa Thoracic, Lumbar Spine	None	Cl: No change Hor: No change PRL 720000 mU/L Rad: No change MRI pituitary	Died 5 months after spinal mets noted (6 months after initiation of chemotherapy)
(3) PRL	CCNU/5-FU × 6	Frontal lobe Parietal lobe Orbit (left)	None	Cl: Vision improved Hor: No change PRL 45000 mU/L Rad: No change CT pituitary	Died 11 yr after CNS mets noted (11 yr post-chemotherapy)
	Carboplatin × 5		None	Cl: No progression Hor: PRL ↓ from 97000 to 79000 mU/L Rad: No change CT pituitary	
	Carboplatin × 3		None	Cl: Deterioration of vision Hor: No change in PRL levels Rad: ? Reduction tumor size	
	5-FU/α-INF × 8		Epilepsy WBC ↓	Cl: no progression. ? Improved Hor: PRL ↑ from 400000 to 641000 mU/L Rad: No change CT pituitary	
	Carboplatin/α-INF × 4		WBC ↓	Cl: Worsening cerebral function Hor: PRL 350000 mU/L Rad: Progression	
(4) ACTH (ng/L)	CCNU/5-FU × 6 cycles	Thoracic spine Liver	Nausea	Cl: No change Hor: ACTH from 500 to 472 ng/L Rad: No change in size	Died 18 months after spinal mets noted (3 yr postchemotherapy)
	Carboplatin × 6			Cl: Visual deterioration Hor: ACTH ↑ from 1892 to 2951 ng/mL Rad: Progression	
	DTIC × 2			Cl: Deterioration Hor: ACTH 3000 ng/L Rad: Progression	
(5) PRL	CCNU/5-FU × 2 cycles	Retrosellar and brainstem extensions	None	Cl: Improvement Hor: PRL ↓ from 21078 to 4746 mU/L Rad: Reduction in size	Died from other cause (6 months after initiation of chemotherapy)
(6) GH (mU/L)	CCNU/5-FU × 2 cycles	Max extension into cavernous sinus (right)	None	Cl: Uncontrolled acromegaly Hor: No change in GH levels Rad: No change in size	Alive (5 yr after initiation of chemotherapy)
(7) ACTH	CCNU/5-FU × 4 cycles	Pituitary fossa and both cavernous sinuses	None	Cl: No change in pigmentation Hor: No change in ACTH levels Rad: No change in size	Alive (4 yr after initiation of chemotherapy)
	Carboplatin/5-FU × 6		Microscopic hematuria	Cl: No change in pigmentation Hor: No change in ACTH levels Rad: No change in size	

Cl, Clinical; Hor, Hormonal; Rad, Radiological response; α-INF, α interferon; CCNU, Lomustine; 5-FU, 5-flourouracil; DTIC, Dacarbasine; WBC, Wight blood cells; PRL, mU/L=20 ng/mL; ARDS, Adult Respiratory Distress Syndrome.

and/or presence of the symptoms was similar to that seen in patients with more benign tumors. Only patient 2 presented with hypopituitarism; none of the patients had developed diabetes insipidus. The median age at presentation was 32 yr (range, 23–48 yr). All patients presented with macroadenomas; when high resolution scans were available (patients 1, 4, 5, and 7), there was radiological evidence of invasion (21). Table 1 shows the clinical, hormonal, and radiological details of all patients on presentation.

All patients had initial treatment with either surgery, [transsphenoidal (n = 4) or transcranial (n = 2)] followed by external beam radiotherapy (n = 7) or in one case (patient 2) radiotherapy alone. All patients had invasive tumors infiltrating adjacent tissues confirmed by operative findings. Patients with prolactinomas showed either initial or delayed resistance to a variety of dopamine agonists, and PRL levels were characteristically elevated to above 100,000 mU/L (5,000 ng/mL). The standard therapeutic modalities applied failed to control the disease in all patients. The two patients with Cushing's disease underwent adrenalectomy to obtain control of the hypercortisolemia, as medical adrenolytic therapy had failed, before any evidence of malignant transformation. Patient 2 had already developed spinal metastases before the initiation of chemotherapy.

The chemotherapeutic regimens used and the response to chemotherapy are shown in Table 2. No chemotherapy-related deaths were observed. The combination of CCNU/5-FU was given to all seven patients, with a median of 2 cycles (range, 1–6 cycles). CCNU/5-FU therapy was associated with minimal toxicity and/or specific side-effects; only 1 patient developed mild nausea. Patients 1 and 2 died within 3 months after the initiation of treatment, whereas patients 3 and 4, who both received 6 full courses of chemotherapy, survived for 52 and 63 months, respectively. Patient 1 had achieved a 3-yr disease-free interval after initial chemotherapy with etoposide and *cis*-platin. He then obtained a greater than 50% reduction in hormonal secretion after CCNU/5-FU, but 1 month after completing his second course of chemotherapy he developed evidence of systemic metastases, and the treatment was discontinued. Patient 3 achieved a partial symptomatic response (6 months), although this was not associated with any hormonal or radiological improvement. Only patient 5 obtained a clinical, hormonal, and radiological response (Fig. 1), but subsequently relapsed and died 6 months later from cardiorespiratory arrest. Patients 3, 4, and 7 received further different chemotherapeutic regimens in an attempt to achieve disease control. The administration of carboplatin at a dose of 360 mg/m^2 (median, 6 courses; range, 6–11 courses), either alone or in combination with 5-FU (8 cycles) or interferon-α (12 cycles), failed to achieve a response. In 1 case, patient 3, chemotherapy with carboplatin led to a moderate reduction of serum prolactin (while the patient was taking a stable dose of dopamine agonists), but had to be discontinued after a reduction in platelet count (11 $\times$ courses of carboplatin of 360 mg/m^2 each). Furthermore, the administration of interferon-α in the same patient was associated with severe side-effects, an epileptic fit (probably due to inappropriate vasopressin secretion), and neutropenia. Three of the patients (no. 1, 2, and 4) developed progression of the disease during treatment. Clinical symptoms/signs at malignant transformation in the 4 patients, with a median interval from original diagnosis of 12 yr (range, 8–19 yr), were similar to those at initial presentation. Standard histopathological features did not change during the course and/or progression of the disease.

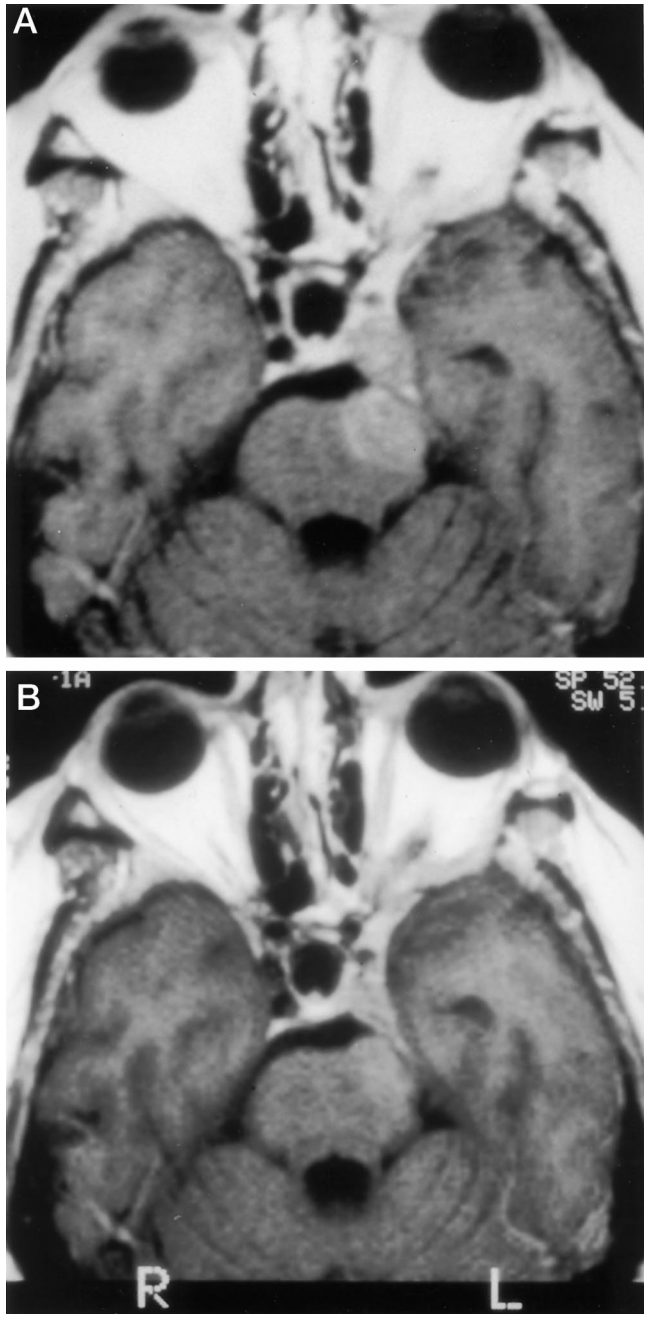

FIG. 1. Reduction of tumor size, retrosellar (pontine) extension, and cavernous sinus invasion (computed tomography scan) in a patient with a highly aggressive prolactinoma before (a) and after (b) two courses of chemotherapy with CCNU/5-FU.

Discussion

The majority of large and locally aggressive pituitary tumors respond to conventional treatment with surgery (transsphenoidal and/or transfrontal), external beam radiotherapy

(6), and hormonal manipulation with dopamine agonists, somatostatin analogs, or occasionally tamoxifen (14, 15). However, such treatment has been shown to exert little influence in the progress of the disease for large, locally recurrent and highly aggressive or frankly malignant pituitary tumors (14, 15, 22, 23), with the exception of a few case reports where bromocriptine successfully reduced PRL levels with (23) or without (24, 25) reduction of tumor mass. The somatostatin analog octreotide has not been shown to have any consistent effect on aggressive tumor growth, although it may reduce hormonal secretion (22) and exert a major analgesic effect (26), whereas tamoxifen has produced conflicting results in the management of malignant prolactinomas (15, 23).

We have therefore used chemotherapy in patients with recurrent and highly aggressive tumors and in patients with CNS or systemic metastases, although the published literature reports only occasional and short lasting responses (11–14). Based on previous observations of other neuroendocrine tumors responding to the combination of a nitrosourea and 5-FU (18) as well as our own initial experience (19), we have used the combination of CCNU and 5-FU in three patients with highly aggressive pituitary tumors and four patients with metastatic malignant pituitary tumors; all of these patients had functioning tumors. One of our patients (patient 3) had previously received platinum- based chemotherapy with a more durable partial response than we have observed in the seven patients treated with 5-FU/CCNU. Of these three patients, all of whom received single agent (carboplatin) after failure to respond to 5-FU/CCNU, there was one marker response (PRL) but no objective tumor shrinkage in any of the subjects, and there was definite progression in one case. This point is of particular interest, as there are data showing good efficacy of such chemotherapy in other neuroendocrine tumors (27). As our data indicate a suboptimal response to 5-FU/CCNU, it is possible that *cis*-platinum-based chemotherapy should be first line in these patients.

All seven patients reported here had secretory adenomas, in contrast to the 30% prevalence of nonsecretory adenomas in our database; even so, no nonfunctioning tumors are presented in this series. This is also concordant with the observations of Brada *et al.* (28) that patients with secretory adenomas may have a less favorable prognosis. This is also evident in a recent review of all published patients with pituitary carcinomas (29).

Four patients had malignant tumors (a prevalence of 0.2% in our series of pituitary tumors), which is in agreement with previous reports (9, 10). Given the rarity of the disease we have recently reviewed all published cases, including our own, of pituitary carcinomas and monitored their outcome (29). All of the present four patients with malignant tumors died as a consequence of the disease; patients with existing systemic metastases died within a few months after the initiation of chemotherapy, whereas two patients to whom chemotherapy was administered before metastases became evident survived 52 and 63 months, respectively. One of the patients with an aggressive tumor, a prolactinoma, showed an apparent response to treatment, but she subsequently relapsed and died 6 months after the conclusion of two courses of chemotherapy. Two other patients with aggressive tumors did not show any consistent responses to chemotherapy, although the disease remained stable. The patients who responded and showed prolonged survival received chemotherapy, which was initiated early in the course of the disease before metastases were demonstrable. Furthermore, a subsequent patient with a metastatic prolactinoma experienced a 3-yr survival after initial chemotherapy with a platinum-based regimen. No chemotherapy-induced deaths or major chemotherapy related side-effects were noted. Another patient developed apparent clinical remission but without tumor marker or radiological responses. A tumor marker response was observed in another patient, but was not associated with reduction of the size of the tumor as previously noted (15, 30, 31). This may reflect partial response to chemotherapy or possibly dedifferentiation of the neoplastic cells, a feature that has been described in other neuroendocrine tumors (22).

In an attempt to achieve disease control, several researchers have used in the past systemic chemotherapy in aggressive and malignant pituitary tumors. Vaughan *et al.* (32) treated a patient with an invasive corticotroph tumor, who had already received maximum treatment with radiotherapy, with a chemotherapy regimen based on procarbazine, etoposide, and CCNU. At follow-up 1 yr later, the patient had stable disease (32). The combination of CCNU and doxorubicin was given to a patient with an aggressive GH-secreting tumor with clinical, hormonal, and radiological responses; furthermore, 2 yr after the initial treatment, the patient was in sustained remission (33). The rationale for using the above chemotherapeutic drugs was based on their ability to cross the blood-brain barrier (33), although there is evidence to suggest that this may already be altered in patients with pituitary tumors (6).

Reports concerning responses to chemotherapy in patients with frankly malignant pituitary tumors are more conflicting (29). Kaizer *et al.* (34) described a patient with a malignant corticotroph-secreting tumor who responded to the combination of cyclophosphamide, doxorubicin, and 5-FU with initial stabilization but later regression of the metastatic deposits. A GH-secreting carcinoma with CNS metastases has also been reported that apparently responded to the combination of methotrexate and 5-FU; subsequent follow-up after 2 yr did not reveal any tumor recurrence. Initial responsiveness of a PRL-secreting carcinoma with CNS metastases to CCNU, procarbazine, and etoposide (14) and that of a TSH-secreting tumor to 5-FU and adriamycin (22) were followed by recurrence and disease progression. In most reports, few patients have survived for more than 1 yr (13), and most have responded poorly to chemotherapy. We have also reviewed all published cases of pituitary carcinomas who received some form of cytotoxic chemotherapy and their responses to treatment (29). Of interest is the finding that the majority of patients with malignant pituitary tumors and extra-CNS metastases who were still alive at follow-up (12, 13, 23, 34, 35) had received some form of cytotoxic chemotherapy. This observation and the apparent response to chemotherapy of some patients with aggressive tumors with either regression or stabilization of the disease may justify the early use of chemotherapy in patients with recurrent highly aggressive

and potentially malignant tumors who have already received maximum therapy with surgery and radiotherapy (36).

In summary, response to chemotherapy in patients with pituitary carcinomas and established metastases is generally poor, with most patients dying within 1 yr despite maximum treatment. However, the early use of chemotherapy may still be of value in some patients with recurrent highly aggressive tumors once they have recurred, besides maximum therapy with surgery and radiotherapy. The combination of CCNU/5-FU, although well tolerated, was associated with a poor response rate overall in terms of tumor shrinkage, but clinically valuable responses were seen in some patients, albeit temporarily. We would currently recommend that CCNU/5-FU may still be used for relatively indolent tumors in the first instance. However, for patients refractory to this treatment or for those whose tumors show highly aggressive or frankly malignant characteristics, we are now using a platinum-based regimen in association with etoposide. New clinical trials to assess optimal schemes (perhaps based on *cis*-platinum) are necessary until more specific treatment is available.

References

1. **Molitch ME, Russell EJ.** 1990 The pituitary incidentaloma. Ann Intern Med. 112:925–931.
2. **Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH.** 1994 Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med. 120:817–820.
3. **Moertel CG, Rubin J, Kvols LK.** 1989 Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. J Clin Oncol. 7:865–868.
4. **Faglia G.** 1993 Epidemiology and pathogenesis of pituitary adenomas. Acta Endocrinol (Copenh). 129:1–5.
5. **Shelman WR, Laws ER, Scheithauer BW, Carpenter SM.** 1986 The occurrence of dural invasion in pituitary adenomas. J Neurosurg. 64:402–407.
6. **Price PA.** 1992 Cytotoxic chemotherapy for aggressive pituitary tumours. In: Grossman A, ed. Clinical endocrinology. Oxford: Blackwell; 235–237.
7. **Scheithauer BW, Kovacs KT, Laws ER, Randall RV.** 1986 Pathology of invasive pituitary tumours with special reference to functional classification. J Neurosurg. 65:733–744.
8. **Doniach I.** 1992 Pituitary carcinoma. Clin Endocrinol (Oxf). 37:194–195.
9. **Doniach I.** 1997 Pituitary carcinoma. In: Sheaves R, Jenkins PJ, Wass JAH, eds. Clinical endocrine oncology. Oxford: Blackwell; 225–227.
10. **Beauchesne P, Trouillas J, Brral F, Brunon J.** 1995 Gonadotropic pituitary carcinoma: case report. Neurosurgery. 37:810–816.
11. **Mountcastle RB, Roof BS, Mayfield RK, et al.** 1989 Case report: pituitary adenocarcinoma in an acromegalic patient: response to bromocriptine and pituitary testing: a review of the literature on 36 cases of pituitary carcinoma. Am J Med Sci. 298:109–118.
12. **Pernicone PJ, Scheithauer BW, Sebo TJ, et al.** 1997 Pituitary carcinoma: a clinicopathological study of 15 cases. Cancer. 79:804–812.
13. **Assai A, Matsutani M, Nobuaki F, Tarakura K.** 1988 Malignant growth hormone-secreting pituitary adenoma with haematogenous dural metastasis: case report. Neurosurgery. 22:1091–1094.
14. **Peterson T, McFarlane IA, McKenzie JM, Shaw MD.** 1992 Prolactin secreting pituitary carcinoma. J Neurol Neurosurg Psychol. 55:1205–1206.
15. **Walker JD, Grossman AB, Anderson JV, et al.** 1993 Malignant prolactinoma with extracanial metastases: a report of three cases. Clin Endocrinol (Oxf). 38:411–419.
16. **Trainer PJ, Besser GM.** 1995 The Bart's endocrine protocol book. London: Churchill Livingstone; 3–17.
17. **Moertel CG.** 1987 An odyssey in the land of small tumours. J Clin Oncol. 5:1503–1523.
18. **Moertel CG, Leukopoulo M, Lipitz S, Hahn R, Klassen D.** 1992 Streptozocin-doxorubicin, streptozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med. 326:519–523.
19. **Harris PE, Bouloux PMG, Wass JAH, Besser GM.** 1990 Successfull treatment by chemotherapy for acromegaly associated with ectopic growth hormone releasing hormone secretion for a carcinoid tumour. Clin Endocrinol (Oxf). 32:315–321.
20. **Hamilton RJ, Sweney P, Rubin SJ, Dujovry M, Pelizzari CA, Chen GT.** 1995 Comparison of static conformal field with multiple noncoplanar arc techniques for stereotactic radiosurgery or stereotactic radiotherapy. Int J Radiot Oncol Biol Phys. 33:1221–1228.
21. **Hardy J.** 1979 Transphenoidal microsurgical treatment of pituitary tumours. In: Linfoot J, ed. Recent advances in the diagnosis and treatment of pituitary tumours. New York: Raven Press; 375–378.
22. **Mixson AJ, Friedman TC, Katz DA, et al.** 1993 Thyrotropin-secreting pituitary carcinoma. J Clin Endocrinol Metab. 76:529–533.
23. **Golland R, Kosty M, Cheney C, Copeland B, Bordin G.** 1995 Prolactin secreting pituitary carcinoma with implants in the cheek pouch and metastases to the ovaries. Cancer. 76:1814–1820.
24. **Popovic EA, Vattuone JR, Siu KA, Busmanis I, Pullar MJ, Dowling J.** 1991 Malignant prolactinomas. Neurosurgery. 29:127–130.
25. **Muhr C, Bergstom M, Lundberg PO, et al.** 1988 Malignant prolactinoma with multiple intracranial metastases studied with positron emmision tomography. Neurosurgery. 22:374–379.
26. **Yin KJ.** 1995 Distribution of somatostatin mRNA containing neurons in the primary pain relaying nuclei in the rat. Anat Rec. 241:579–584.
27. **Hatton MQF, Reed NS.** 1997 Chemotherapy for neuroendocrine tumors: the Beatson oncology centre experience. Clin Oncol. 9:385–389.
28. **Brada M, Ford D, Traish D, et al.** 1993 The long term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clin Endocrinol (Oxf). 38:571–578.
29. **Kaltsas GA, Grossman, AB.** 1998 Malignant pituitary tumours. Pituitary. 1:69–81.
30. **Murphy FY, Vesely DL, Jordan RM, Flanigan S, Kohler PO.** 1987 Giant invasive prolactinomas. Am J Med. 83:995–1002.
31. **Davis JRE, Sheppard MC, Heath DA.** 1990 Giant invasive prolactinoma: a case report and review of nine further cases. Q J Med. 74:259–264.
32. **Vaughan NJA, Laroche CM, Goodman I, Davies MJ, Jenkins JS.** 1985 Pituitary Cushing's disease arising from a previously non-functional corticotrophic chromophobe adenoma. Clin Endocrinol (Oxf). 22:147–153.
33. **Kasperlik-Zaluska AA, Wislawski J, Kaniewska J, Zborzil J, Frankiewicz E, Zgliczynski S.** 1987 Cytostatics for acromegaly. Marked improvement in a patient with an invasive pituitary tumour. Acta Endocrinol (Copenh). 116:347–349.
34. **Kaizer FE, Orth DN, Mukai K, Oppenhaimer JH.** 1983 A pituitary parasellar tumour with extracranial metastases and high, partially suppressible levels of adrenocorticotropin and related peptides. J Clin Endocrinol Metab. 57: 649–653.
35. **Frost AE, Tenner S, Tenner M, Rollhauser C, Tabbara SO.** 1995 ACTH-producing pituitary carcinoma presenting as a cauda equina syndrome. Arch Pathol Lab Med. 119:93–96.
36. **Kuvoki M, Tanaka R, Yokoyama M, Shimbo Y, Ikuta F.** 1987 Subarachnoid dissemination of a pituitary adenoma. Surg Neurol. 28:71–76.