Cancer Chemotherapy and Biological Response Modifiers Annual 10
H.M. Pinedo, D.L. Longo and B.A. Chabner, editors

CHAPTER 19

Endocrine tumors

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The clinical efficacy of the treatment with somatostatin in patients with diverse endocrine tumors is a very interesting finding. New data concerning the application of the long-acting somatostatin analog SMS 201-995, especially in patients with carcinoid tumors and acromegaly, appeared this year.

In the treatment of patients with pituitary tumors the clinician is often confronted with the choice between surgery and the administration of bromocriptine or somatostatin. The advantages of each treatment modality are discussed below.

Since the combination of streptozotocin and 5-fluorouracil is the only known effective drug regimen in endocrine tumors, several authors conducted trials with other cytostatic drugs. Results are described in this Chapter.

CARCINOID AND OTHER NEUROENDOCRINE GUT TUMORS

Carcinoid of the appendix is usually not recognized until the appendix is removed for other reasons and sectioned. Simple appendectomy has generally been accepted as adequate treatment, although in some cases, especially in younger patients, right hemicolectomy was performed. The characteristics of 150 consecutive patients with carcinoid tumors of the appendix seen from 1930 to 1966, in whom appendectomy was performed for other reasons, were analyzed by Moertel et al [1]. No metastases were observed at the first operation among 127 patients with appendiceal carcinoids with a diameter of less than 2 cm in largest dimension, while 3 of 14 patients with lesions 2–3 cm in largest dimension and 4 of 9 patients with lesions greater than 3 cm developed metastases. Among 122 patients with apparently localized tumors with a diameter less than 2 cm who were available for follow-up, no recurrence or metastases were observed for a median time of more than 26 years. Among the 23 patients who had carcinoids with a diameter greater than 2 cm, 4 had unresectable metastases at the time of original diagnosis. Twelve of these 23 patients were treated with simple appendectomy. One of them had a local recurrence with resectable metastases 29 years later. Seven patients were initially treated with hemicolectomy and 2 of them were found to have microscopic metastases in regional nodes. All 7 were free of recurrence after a median follow-up of 11 years. There was no discernable difference between metastatic and nonmetastatic cases in cellular morphology and architecture. Two of the 7 patients with metastases had invasion of the mesoappendix, whereas only 4 of 39 patients without metastases had this feature.

According to these results patients with tu-

mors with a diameter smaller than 2 cm had 100% chance of cure presumably with appendectomy alone. Right hemicolectomy seems justified only in young patients with tumors greater than 2 cm who have a low risk of operative morbidity or mortality.

The characteristics of somatostatin and its long-acting analog SMS 201-995 (Sandoz) were discussed in the previous Annual [2]. Somatostatin inhibits the release of most regulatory gut peptides and exocrine pancreatic, gastric and intestinal secretions. It also suppresses tumoral secretions by pancreatic and gut endocrine tumors and is therefore used in the treatment of the carcinoid syndrome.

Souquet and colleagues reported the therapeutic effect of SMS 201-995 given twice daily over a period of 2–12 months to 9 patients with pancreatic apudomas and 9 with metastasized carcinoid tumors [3]. In 7 patients with gastrinomas SMS 201-995 decreased plasma gastrin levels in all but 1 patient. In 1 glucagonoma patient, glucagonemia and skin lesions disappeared. In the patients with metastasized carcinoid, control of carcinoid syndrome was partial and inconsistent. No antitumoral effect was seen in these 18 patients.

Van Houten et al [4] observed good control of progressive diarrhea with SMS 201-995 in a 68-year-old man suffering from malignant carcinoid syndrome. This patient was refractory to therapy with 5-fluorouracil, streptozotocin and mitoxantrone. In this patient no cytotoxic effect of SMS 201-995 was seen.

A similar good palliative result was achieved in an elderly man presenting with severe watery diarrhea and anemia due to pancreatic vipoma [5]. SMS 201-995 50 μg twice daily improved his symptoms for 24 months. Plasma levels of vasoactive intestinal peptide (VIP) decreased but did not normalize. No regression of tumor size occurred.

Besides serotonin and bradykinin, carcinoid tumors can produce more than 20 substances which influence vascular, bronchial and gastrointestinal activity. For this reason patients can experience difficulties with anesthesia. Roy and coworkers described a patient with carcinoid syndrome who received long-term antiserotonin therapy with parachlorophenylalanine. She experienced a flushing attack with hypotension during the prophylactic administration of aprotinin prior to the induction of anesthesia. When she was subsequently prepared with SMS 201-995, anesthesia for hepatic resection was uneventful [6].

Padfield encountered the same difficulties when a 47-year-old man with symptomatic carcinoid pretreated with ketanserin 2 times daily 80 mg was anesthetized. The same patient, having had pretreatment with parachlorophenylalanine 500 mg 4 times daily and cyproheptadine in addition to ketanserin, was anesthetized a week later without difficulties [7].

In summary, the long-acting somatostatin analog SMS 201-995 is effective in controlling clinical symptoms of a majority of patients with carcinoid syndrome and other neuroendocrine gut tumors. Since administration of 50 μg twice daily provokes only mild side effects, this approach is worthwhile in all patients in whom no surgical resection can be undertaken.

SMS 201-995 appears to be highly effective in preventing hemodynamic problems during anesthesia in patients with metastasized carcinoid.

PITUITARY ADENOMAS

The traditional forms of therapy for pituitary tumors have usually included surgery, irradiation, or both. Presently other options should be considered such as somatostatin and bromocriptine.

Factors influencing the outcome of transsphenoidal surgery for prolactinoma and nonfunctioning pituitary tumors, including the role of preoperative bromocriptine therapy, were

analyzed by Bevan and coworkers [8]. Radical trans-sphenoidal surgery in 58 patients with large nonfunctioning pituitary tumors relieved pressure symptoms without loss of pituitary function. Eight patients were pretreated with bromocriptine for up to 48 weeks. No shrinkage of these tumors were observed. In 20 patients with noninvasive macroprolactinomas, radical surgery caused no loss of pituitary function but cured 8 of them, 1 of whom has relapsed. None of 8 invasive prolactinomas was cured by surgery.

Preoperative treatment with bromocriptine caused a marked reduction in the size of the tumor in 7 of 7 patients with prolactinomas, but if continued beyond 6 weeks induced tumor fibrosis and uneven shrinkage which made surgery dangerous and unproductive. Patients with microprolactinomas did not benefit from surgery compared with those who received conservative treatment [8].

Bromocriptine is known to be effective in the acute treatment of large macroprolactinomas. Zarate et al [9] observed rapid amelioration of the clinical and visual defects in 6 of 6 patients who were treated with long-acting bromocriptine in a dosage of 50 mg as a single intramuscular injection.

Several questions concerning the treatment of prolactinomas with bromocriptine have not been answered. No reports on long-term toxicity have appeared and it is not sure if the serum prolactin level always rebounds after cessation of therapy. Dalzell and coworkers observed normal growth and pubertal development in an 11-year-old male during bromocriptine treatment of a prolactin-secreting pituitary macroadenoma. This suggests that bromocriptine may also be considered as initial therapy in the management of prepubertal patients with prolactinomas [10].

SMS 201-995 has also been used in the preoperative management of patients with acromegaly and in those patients who are refractory to surgery and radiotherapy. Spinas et al [11] treated 5 acromegalic patients preoperatively over a period of 1–4 weeks with 100 μg SMS 201-995 3 times daily subcutaneously. This resulted in a rapid improvement of the clinical symptoms in 4 of 5 patients. In these same patients plasma growth hormone concentrations decreased markedly, but normalized only in 1 patient. Tumor volume decreased in 1 patient. All tumors appeared extraordinarily soft upon operation. The authors conclude that somatostatin causes softening of adenomas, helps to delineate the borders of adenomas and renders it possible to save healthy pituitary tissue.

Although somatostatin is supposed to be ineffective in the acute relief of pressure symptoms, Guillausseau and colleagues reported that SMS 201-995 was effective in the rapid disappearance of visual abnormalities in a patient with a thyrotropin-secreting pituitary adenoma where bromocriptine was shown to be ineffective [12]. George et al [13] studied the effect of SMS 201-995 on blood growth hormone levels and tumor morphology in a 36-year-old previously untreated acromegalic woman. Treatment with 50 μg subcutaneously 3 times daily resulted in a marked suppression of plasma growth hormone level. After 10 days of treatment the tumor was removed by trans-sphenoidal surgery and analyzed by histology, immunohistochemistry and morphometry. The nuclear and cytoplasmic areas of the adenoma subjected to SMS 201-995 treatment were smaller and the lysosomes occupied more of the cytoplasmic volume than those of controls. The absence of necrosis suggests that SMS 201-995 has no direct cytotoxic effect and that functional inhibition is involved.

Chiodini and coworkers studied the effect of acute and chronic subcutaneous administration of SMS 201-995 in acromegalic patients. The results were compared with those obtained in the same patients treated with oral bromocriptine. A single dose of 50 μg SMS 201-995 administered

to 28 patients induced a more rapid, greater and more prolonged reduction in plasma growth hormone levels than did 2.5 mg bromocriptine. Chronic treatment with SMS 201-995 100–300 μg/day induced in 16 patients a significantly greater decrease in mean plasma growth hormone and somatomedin C levels than did 20 mg bromocriptine. Combined treatment with the 2 agents had an additive effect [14].

SMS 201-995 has also been shown to be effective in lowering serum levels of thyrotropin in 4 of 5 patients suffering from a more infrequent manifestation of pituitary adenoma, a thyrotropin-secreting adenoma [15]. Levels of another tumor marker, the subunit of α-thyrotropin, were reduced in all 5 patients.

In summary, surgery is the treatment of choice for nonfunctioning pituitary tumors. Microprolactinomas probably do not require treatment, unless they are symptomatic. For other prolactinomas surgery is the first choice. Pretreatment with bromocriptine may render these tumors more resectable. Bromocriptine is the first drug in the acute treatment of pressure symptoms of functioning pituitary adenomas. SMS 201-995 is highly effective in treatment of symptomatic acromegalic patients refractory to surgery and radiation. Long-term toxicity studies are lacking in order to evaluate whether bromocriptine and SMS 201-995 are safe as primary treatment for prolactinomas and acromegaly, respectively.

CHEMOTHERAPY IN ENDOCRINE TUMORS

Results of chemotherapy in patients with endocrine tumors are poor. The most widely used regimen of streptozotocin and 5-fluorouracil gives response rates of about 20%. The Eastern Cooperative Oncology Group compared the combination of 5-fluorouracil and streptozotocin with cyclophosphamide and streptozotocin in a randomized trial in patients with metastatic carcinoid tumors. The response rates for the 2 arms were 33% (14/42) and 26% (12/47), respectively [16].

The Southwest Oncology Group conducted a prospective trial in patients with metastatic carcinoid tumors with a combination therapy including 5-fluorouracil, doxorubicin, cyclophosphamide and streptozotocin (FAC-S) or the same combination without doxorubicin (FC-S) in patients with heart disease. Fifty-six patients received FAC-S and 9 received FC-S. The response rates were 31% and 22%, respectively. Responses were generally partial and of brief duration [17].

A Phase II study of cisplatin therapy in 15 patients with metastatic carcinoid tumors conducted by Moertel and coworkers showed only 1 very transient partial and hormonal response that was not associated with symptomatic improvement [18].

Another Phase II study using VP-16 150 mg/m^2/d (Days 1, 3 and 5, with cycles repeated every 21 days) was carried out by Kelsen et al [19] in 19 patients with apudomas (islet cell, carcinoid or medullary carcinoma of the thyroid). Four partial responses were seen.

Ahuja and Ernst reported the results of chemotherapy in 8 patients with metastasized thyroid carcinomas. Six cases received a doxorubicin-containing regimen. A partial regression of pulmonary metastases was only achieved in the 2 patients treated with the combination doxorubicin/bleomycin, one having an undifferentiated spindle and giant cell carcinoma, the other having a Hürthle cell carcinoma. The other patients (2 medullary carcinomas, 1 papillary carcinoma, 1 anaplastic carcinoma and 1 undifferentiated spindle and Hürthle cell carcinoma) receiving cyclophosphamide and vincristine did not improve [20].

The efficacy of o,p′-DDD (mitotane) in patients with hormone-producing adrenocortical

cancer was reported in the previous Annual [2]. Eriksson and colleagues treated 3 patients with advanced adrenocortical carcinoma with a combination of intermittent streptozotocin and a relatively low continuous dose (2–4 g/day) o,p′-DDD. Two patients were treated preoperatively and the primary tumors, initially considered inoperable, could be resected after 19 and 5.5 months, respectively. In the patient with the longer treatment (35 mths) lung and lymph node metastases had disappeared and she had no evidence of recurrent disease 6.5 years after start of the therapy [21].

Rostu et al [22] studied the neurotoxicity of o,p′-DDD treatment in 5 patients with adrenocortical carcinoma and 7 patients with Cushing's syndrome. All presented with neurological symptoms and half of them had major complications. There was no relation between the occurrence of these symptoms and the dose and duration of o,p′-DDD therapy.

CONCLUSIONS

Endocrine tumors are rare tumors. Many of the above studies are anecdotes which do not help much in learning how to manage these patients. Surely this is an area where intercenter collaboration is necessary so that some properly designed studies can be conducted to answer specific questions.

The scarce reports on chemotherapy in endocrine tumors this year are not very promising. In the last Annual good results were reported using interferon, meta-iodobenzylguanidine and SMS 201-995 in patients with apudomas. The efficacy of SMS 201-995 was confirmed by several authors, especially in patients with metastatic carcinoids. Several studies with interferon and meta-iodobenzylguanidine are underway. Progress in treatment results of patients with metastasized endocrine tumors will probably come from these sources.

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