Progress in the management of solid tumours

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Carcinoid tumours

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Summary

The use of long-acting and potent somatostatin analogues is a major advance in the management of carcinoid tumours. In addition to providing effective symptom relief in malignant carcinoid syndrome, octreotide can also be used for diagnostic purposes. Despite its expense, octreotide is the current agent of choice for the treatment of this condition while analogues with different receptor specificities and pharmacokinetics hold promise for the future. Gastric carcinoids have aroused interest because of their experimental association with chronic hypergastrinaemia, a condition now commonplace because of the widespread use of H₂-blockers and proton-pump inhibitors. This subject is reviewed. The slow evolution of many tumours demands prolonged follow-up and the active use of a variety of palliative interventions. These include measures such as hepatic and cardiac surgery, which might be deemed inappropriate for patients with other types of metastatic malignancy. Interferons may have a role when first-line treatments have failed. Chemotherapy is, generally, of limited value.

Keywords: carcinoid tumours, neuroendocrine tumours, octreotide, somatostatin analogues

Since their formal recognition at the beginning of this century, it has become increasingly clear that carcinoids form only a part of a spectrum of neuroendocrine tumours; in addition to histological similarities, they have in common the ability to synthesize, and often secrete, a variety of neuroamines and neuropeptides (box 1). Carcinoid tumours have been reported in virtually every site in the body but arise mainly in organs of fore-, mid-, and hindgut (endodermal) origin. Of these, midgut tumours are by far the most common (box 2), occurring in about 1 per 100 000 individuals.¹ Nevertheless, it is noteworthy that extra-gastrointestinal tumours are being detected more frequently than before. For example, pulmonary carcinoids may constitute up to 30% of all carcinoids, a figure three times greater than earlier estimates. Readers specifically interested in bronchial carcinoids are referred to a recent review.²

Classification and pathogenesis

Fore-, mid-, and hindgut tumours tend to have characteristic properties (box 3). Their aetiology remains unclear. Current research efforts are focussed on mutations in oncogenes and tumour suppressor genes. Induction of cellular proliferation by paracrine agents and growth factors is believed to follow these mutations. Abnormal p53 oncogene expression has been found in up to 45% of bronchial carcinoids, although this is conspicuously absent in gastrointestinal carcinoids. Amplification of HER-2/neu cellular oncogene expression, whose protein product has homology to the EGF receptor, and of Gs, expression has been detected in ileal and thymic carcinoids, respectively.³

FAMILIAL

Multiple endocrine neoplasia

Carcinoids occur in approximately 9% of patients with multiple endocrine neoplasia, mainly in the type I syndrome. About half are of foregut origin (27% bronchial and 24% thymic).⁴ Only 9% are ileal, and an associated carcinoid syndrome is rare. Interestingly, they are thymic in origin in about 75% of women, and bronchial in 66% of men with this condition.⁵ A linkage with the PYGM locus on chromosome 11 (q13) has been noted in one family.

Non-multiple-endocrine-neoplasia

Non-multiple-endocrine-neoplasia familial carcinoid tumours are rare. In the five families described to date, all the tumours have been gastrointestinal. The presumed genetic abnormalities have not been identified and there is no evidence, as yet, that they represent a *forme fruste* of multiple endocrine neoplasia.

GASTRIC CARCINOIDS

The widespread use of gastric acid inhibitors, notably H₂-blockers and proton-pump inhibitors, has heightened interest in the pathogenesis of gastric carcinoids arising from enterochromaffin-like cells (ECLomas). In the *Mastomys* (rodent) experimental model, gastrin acts as an essential trophic factor on gastric mucosa, and high levels induced by pharmacological inhibition of gastric acid secretion promote the development of multicentric ECL carcinoids. In humans, it seems that long-standing hypergastrinaemia alone is able to evoke cellular dysplasia, but is insufficient, by itself, to produce gastric carcinoids. Multiple small tumours, of low malignant potential, often occur in the gastric body/fundus of patients with chronic atrophic gastritis type A, in which hypergastrinaemia coexists with abnormal gastric mucosa (with or without pernicious anaemia). However, they rarely develop, for example, in patients with hypergastrinaemia due to Zollinger–Ellison syndrome in the absence of an associated abnormality such as multiple endocrine neoplasia.

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ICD8 Classification of carcinoids

Tumours of the diffuse endocrine system which are either benign or have a more favourable prognosis than carcinomas (excluding neuroendocrine tumours of the pituitary, thyroid adrenals and pancreas and neuroendocrine carcinomas)

Histological characteristics

- typical growth pattern
- silver affinity
- expression of neuroendocrine markers
- production of gut/brain peptides and amines

Box 1

Distribution of carcinoids by site

Site	% of total
appendix	44
rectum	15
ileum	12
pulmonary	12
colon	5
small intestine (unspecified)	5
stomach	2
duodenum	2
jejunum	1
ovary	0.5
unknown primary	0.3
miscellaneous	0.2

Adapted from ¹

Box 2

Single large, sporadic lesions, which have greater malignant potential (55% metastatic rate) and may cause an atypical carcinoid syndrome, are not, however, demonstrably linked to chronic hypergastrinaemia.⁹

Investigation

LOCALIZATION

Autopsy studies indicate that about two-thirds of jejunoileal carcinoids remain undetected in life. The vast majority of appendiceal tumours, which comprise 20–60% of all carcinoids, come to light incidentally at appendicectomy. Carcinoid tumours often present as a result of local symptoms (eg, cough, haemoptysis, abdominal pain, gastrointestinal bleeding) and can frequently be identified using routinely employed radiological and/or endoscopic methods. Midgut tumours may give rise to vague abdominal complaints easily attributable to irritable bowel syndrome, and can thus remain undiagnosed for some years.

HORMONAL MANIFESTATIONS

These are not responsible for presentation in the vast majority of cases. They typically relate to the carcinoid syndrome (box 4) which, with few exceptions, only manifests in the presence of hepatic metastases. However, the converse is not true: patients can have extensive liver metastases without having carcinoid syndrome. Carcinoid syndrome complicates up to 10% of midgut tumours, but occurs much less frequently with primaries from other origins; it is rarely, if ever, caused by hindgut tumours. Less commonly, Cushing's syndrome (ectopic adrenocorticotropin and/or corticotropin-releasing factor), syndrome of inappropriate antidiuretic hormone secretion and, rarely, acromegaly (ectopic growth hormone and/or growth-hormone-releasing factor) may occur, most often as a result of occult bronchial tumours. The latter can be notoriously difficult to identify. Syndromes of ectopic hormone secretion require aggressive evaluation and, where necessary, prolonged follow-up to detect the primary tumour.

It is axiomatic that the endocrine diagnosis should be established before further studies are undertaken to localize and sample the tumour. Only carcinoid syndrome is considered here. Flushing is a common cause for

Salient features of carcinoid tumours according to embryological site of origin

Site	Pathology	Peptide/amines	Clinical features
Foregut			
Bronchi, thymus, D1, stomach	Mixed growth pattern, argentaffin -ve, argyrophil +ve, liver, bone metastases (25%)	5-HTP, histamine, ACTH, GH, gastrin	Pulmonary obstruction, atypical flush & hormone syndromes
Midgut			
D2, jejunum, ileum, right colon	Insular growth, argentaffin & argyrophil +ve, liver metastases (60–80%)	5HT, tachykinins, prostaglandins, bradykinin & other hormones	Bowel obstruction, 'typical' pink/red flush, wheeze/diarrhoea if liver metastases (classic carcinoid syndrome)
Hindgut			
Transverse colon to rectum	Trabecular/solid growth, silver staining: as foregut, mainly bone metastases (5–40%)	Local production of SRIF, PYY, glicentin, neurotensin, 5HTP & other peptides	Chance discovery, local symptoms only

Argentaffin +ve: precipitation of silver in absence of reducing agent; argyrophil +ve: precipitation of silver only in presence of reducing agent; SRIF = somatostatin; PYY = peptide YY; 5HT = 5-hydroxytryptamine; 5HTP = 5-hydroxytryptophan; GH = growth hormone; ACTH = adrenocorticotropin; D1 = 1st part of duodenum; D2 = 2nd part of duodenum

Box 3

Clinical features of carcinoid syndrome		
Symptom/sign	Frequency (%)	Characteristics
flushing	84	prolonged/purple (foregut); evanescent/pink-red (midgut)
diarrhoea	70	secretory
dyspnoea	37	due to right heart disease
abdominal pain	33	often long history
proximal myopathy	7	uncommon, often unappreciated
bronchospasm	6	-
dermatosis	5	pellagra: excess tryptophan usage → niacin deficiency
arthropathy	rare	
Adapted from ³⁹		

Box 4

Differential diagnosis of flushing
<ul style="list-style-type: none">• post-menopausal• drug induced: Ca²⁺-channel antagonists, chlorpropamide (+alcohol), disulfiram (+alcohol), iv contrast agents, nicotinic acid• carcinoid syndrome• idiopathic• phaeochromocytoma• systemic mastocytosis/anaphylaxis/-toid reactions (histamine)• medullary thyroid carcinoma• autonomic epilepsy• miscellaneous: skin diseases (acne rosacea), mitral stenosis

Box 5

investigation (box 5). Measurement of 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA, typical reference range: 2–8 mg) remains the screening investigation of choice in most centres. Exclusion of foods rich in serotonin (5-HT) is unnecessary except in borderline positive cases. False negatives may be obtained in patients taking salicylates or L-dopa. As determined by high-performance liquid chromatography and electrochemical detection, 24 h urinary 5-HIAA has a sensitivity and specificity of ~75% and >90%, respectively.⁷ Provocation testing with pentagastrin stimulation has been used when, despite an equivocal biochemical diagnosis, clinical suspicion remains. Most probably, pentagastrin releases endogenous catecholamines which, in turn, can provoke often hazardous flushing. The test should therefore be used with extreme caution (see below). In particular, the standard dose of pentagastrin (0.6 µg/kg intravenously) is unsuitable for patients with, or likely to have, metastatic foregut carcinoids, since it is likely to provoke severe generalised flushing and bronchoconstriction.⁸ An alternative technique that may prove helpful in difficult cases is venous sampling, which may be combined with angiographic visualisation of the tumour.

Other investigations remain research tools and/or have limited availability. They include estimation of platelet 5-HT (more sensitive than urinary 5-HIAA),⁹ general neuroendocrine tumour markers such as chromogranin A (measured as a C-terminal moiety, GAWK, by the UK Supraregional Assay Service), neuron-specific enolase and synaptophysin (limited specificity), and other tumour-derived peptides, such as substance P and neurokinin A. In contrast to midgut tumours, foregut carcinoids tend to produce larger amounts of the 5-HT precursor 5-hydroxytryptophan (5-HTP) than its metabolite 5-HIAA. 5-HT secretion is rare, presumably as a result of aromatic amino acid decarboxylase deficiency. In addition to 5-HTP, measurement of the main histamine metabolite, methylimidazole acetic acid, may also help to identify foregut tumours.¹⁰

IMAGING TECHNIQUES

Computed tomography (CT), magnetic resonance imaging (MRI) and metiodobenzylguanidine (MIBG) scintigraphy readily detect hepatic metastases; MRI may be preferable since it obviates the need for oral contrast media which frequently aggravate any pre-existing diarrhoea. MRI can also visualize bronchial carcinoids that have been missed by CT.

Until recently, MIBG, mainly employed for the diagnosis and treatment of phaeochromocytomas, was the principal radiopharmaceutical used to localize carcinoids. It can be concentrated by a variety of normal tissues, and neuroendocrine and other embryologically related tumours (eg, medullary thyroid carcinoma, neuroblastoma). In addition to its limited specificity and sensitivity (55%),⁵ the advent of radiolabelled octreotide may supersede its future use.

OCTREOTIDE SCINTIGRAPHY

The recognition of somatostatin receptors in a range of neuroendocrine tumours, and the development of octreotide and other long-acting somatostatin analogues, undoubtedly represents the major advance in carcinoid management over the past 20 years. Over 80% of carcinoids have somatostatin receptors.¹¹ In 1989, following its earlier successful use as a therapy for malignant carcinoid syndrome,¹² octreotide was radiolabelled and used to image a variety of tumours scintigraphically. For a number of reasons, such as longer half-life,

Figure 1 Pentreotide scan of neuroendocrine tumour (posterior and anterior views shown in upper and lower panels, respectively). Kidneys are well outlined in posterior view

Conditions associated with accumulation of [^{111}In -DTPA-d-Phe 1]octreotide

- neuroendocrine and related tumours (carcinoid, pituitary, islet, neuroblastoma)
- non-small cell and small cell lung cancer (up to 100%)
- meningiomas (100%)
- breast cancer (> 60% stage I & II)
- granulomatous diseases (sarcoid, tuberculosis, systemic mycoses)
- lymphomas
- renal carcinomas
- external lung irradiation; bleomycin
- recent operation sites
- nasal region and lung hila during flu season (transient)

Box 6

renal clearance, and lower abdominal background, indium (^{111}In), attached to DTPA, has superseded iodine (^{123}I) as the radionuclide of choice. [^{111}In -DTPA-D-Phe 1]Octreotide, also referred to as pentreotide, has the advantage of enabling whole body scanning, theoretically with a resolution of up to 1 mm (tumours with a high density of receptors).¹³ Scanning is best undertaken at 24 and 48 hours after injection, during which time background counts dissipate. Radiation dosage is comparable to thoracic CT scanning (8–16 mSv *vs* 7–11 mSv, respectively).¹⁴ Each scan costs about £500.

[^{111}In -DTPA-D-Phe 1]Octreotide is more sensitive than MIBG in detecting all types of neuroendocrine tumours except pheochromocytomas (96 *vs* 72% sensitivity). In patients with carcinoid tumours fully investigated by other means, pentreotide scanning was found to have 86% and 100% sensitivity, respectively, in detecting the primary and metastases (figure 1). Octreoscans may also reveal unsuspected metastases, or those unrecognised by other imaging methods, in as many as two-thirds of patients.¹⁵ In addition to allowing staging, scanning permits selection of optimal therapy. A positive scan predicts a successful symptomatic response to octreotide treatment¹⁶ and, thus, a better prognosis, whereas a negative one may suggest a more malignant tumour that is best treated with a combination of cisplatin and etoposide.¹⁷

Accumulation of pentreotide is not specific for carcinoids (box 6). It may also occur in a variety of other tumours as well as in several normal tissues (pituitary, thyroid, spleen, liver, kidneys); delayed images may overcome diagnostic difficulty.

Treatment

Curative surgical resection of small, localised primary tumours remains the treatment of choice. In cases of metastatic disease/carcinoid syndrome, surgical and medical palliation can provide excellent symptom relief and considerably improve prognosis. There is no consensus on the timing and extent of surgery. In view of the slow progression of many metastatic tumours, relatively aggressive intervention, including cardiac surgery, may be justifiable. Nevertheless, this same slow pace means that, for many patients, 'no treatment is the best treatment'.¹⁸ Consequently, follow-up needs to be prolonged, particularly since recurrences may occur many years after apparent cure. It is important to emphasize that, although used to judge outcome, tumour markers (eg, urinary 5-HIAA), tumour bulk as assessed by CT/MRI, and symptoms, do not necessarily correlate.

It is generally agreed that the usual histological criteria of malignancy, such as number of mitoses and anaplasia, can be misleading when applied to carcinoid tumours. Malignancy is determined by evidence of invasion and spread, with an apparent progression of local invasion to distant metastasis. Metastatic tendency appears to be linked to tumour size; for example, in hindgut tumours, the risk is less than 2% for those ≤ 1 cm in maximum diameter and over 80% for tumours ≥ 2 cm.¹

Management should also take into consideration the well-documented occurrence of synchronous and metachronous tumours. These have been documented in 7–29% of patients, and are mostly gastrointestinal (especially small bowel) and adenocarcinomas.¹⁹

SURGERY

Appendiceal tumours ≤ 1 cm can be treated by simple appendectomy, whereas those ≥ 2 cm require right hemicolectomy and regional lymphadenectomy. In other locations, the extent of surgery for localised tumours is naturally also, in part, dictated by tumour size.

Gastric carcinoids

Treatment is controversial. For carcinoids associated with type A chronic atrophic gastritis, endoscopic resection and subsequent surveillance has been proposed as first line therapy for tumours <1 cm and which number <5. Antrectomy (to abolish the trophic effect of local gastrin production) is advocated for recurrence or as primary treatment when there are five or more tumours. Excision and antrectomy are recommended for lesions larger than 1 cm, and gastrectomy is advised in the presence of invasive growth or lymph node metastases. Sporadic, solitary, non-chronic atrophic gastritis carcinoids warrant radical surgery because of their relatively aggressive behaviour. Multicentric pre-carcinoids occurring in Zollinger–Ellison/multiple endocrine neoplasia type I syndrome have successfully been managed by intensification of endoscopic surveillance and gastrectomy following the development of macrocarcinoids.¹⁰

Figure 2 CT of same tumour as in figure 1. Bottom CT panel shows primary pancreatic tumour; other lesions are hepatic metastases. Corresponding lesions are shown by matching arrows. (With kind permission of Prof N Peters)

Metastatic tumours

Patients with localised hepatic metastases (~ 1 in 10) have been reported to be cured in 10–25% of cases by hepatic resection.^{7,20} Palliative cytoreduction of at least 90% of the tumour mass may, however, substantially or completely abolish symptoms due to tumour bulk and the carcinoid syndrome, although the duration of effect is variable. A safer alternative is induction of hepatic ischaemia by hepatic artery embolisation²¹ using gelfoam or Ivalon particles (size $< 250 \mu\text{m}$), or, less commonly, by ligation. This approach is purely palliative and has the advantage that embolisation can be repeated if symptoms, due to development of collaterals, reappear.

Limited data are available on hepatic transplantation since it has been undertaken in only a few patients; a preliminary survival time of 13 months has been reported.²² Cluster transplantation of multiple abdominal organs remains a theoretical consideration.

Cardiac surgery

Characteristic echocardiographic abnormalities are demonstrable in 60–70% of patients with malignant midgut carcinoid tumours.²³ Higher levels of urinary 5-HIAA, plasma substance P and neurokinin A have been detected in subjects with the most extensive carcinoid heart disease, but no causal relationship has yet been established. Symptoms of right heart failure, mainly due to tricuspid regurgitation, are an important cause of morbidity and mortality. Right heart disease has been implicated as the cause of death in one-third of subjects with carcinoid syndrome.²⁴ Worthwhile, long-lasting symptomatic and objective improvement can be achieved by reconstructive valvular surgery, although it should be noted that the peri-operative mortality can approach 33%.²⁵ Tricuspid valve replacement, in particular, ought therefore to be considered in carefully selected patients before the onset of significant right ventricular dysfunction.

MEDICAL TREATMENT

The main medical treatments comprise octreotide, interferon, chemotherapy and miscellaneous agents used for symptomatic relief (eg, bronchodilators, codeine). Radiotherapy is reserved for treatment of cord compression or painful bone metastases that are otherwise unresponsive. Internal radiotherapy with MIBG has been used infrequently.

Octreotide

Developed as a long-acting octapeptide analogue of somatostatin, octreotide (SMS 201-995) was first shown to ameliorate carcinoid diarrhoea in 1980.²⁶ In addition to this symptom, octreotide is particularly effective at abolishing flushing. Bronchospasm and other symptoms are more variable in their responses. Objective and symptomatic improvement (50% decrease in tumour markers, decreased tumour bulk and symptoms) occurs in over 70% of patients, for a median duration of 12 months.¹² Retrospective comparison with a cohort of patients treated with chemotherapy, has shown that octreotide improves survival about three-fold²⁷; this has not been confirmed prospectively. Octreotide has also been successfully used for treatment of ectopic adrenocorticotropin syndrome due to bronchial carcinoid tumours.²⁸

The prediction of clinical benefit from chronic therapy with somatostatin analogues following a positive pentreotide scan is correlated with the presence of tumour cell somatostatin receptors. Of the five G-protein-coupled receptor subtypes so far identified (two subgroups: sst 1 and 4 and sst 2, 3, and 5), sst 2 and sst 5 have the highest affinity for octreotide; the former is believed to mediate most of its therapeutic effects.²⁹ A corollary is that a 'false negative' scan and heterogeneous therapeutic responses may be due to the presence of other receptor subtypes. Loss of therapeutic response during chronic octreotide therapy is a well-recognised phenomenon. It generally conforms to one of two patterns, both of which have been ascribed to altered receptor function or expression: early (down-regulation of somatostatin receptors, restorable by a drug-free interval) and eventual escape (development of receptor-negative clones). Occasionally, tumour growth may continue despite ongoing anti-secretory effects, suggesting these actions may be mediated by distinct receptors.

Cellular actions Although octreotide can shrink both primary and metastatic tumours, its antiproliferative effect is not pronounced. It acts by a direct antimitotic action (eg, tyrosine phosphatase activation), additive with cytotoxic agents *in vitro*, altering hormone and growth factor release or action, inhibition of angiogenesis, and modulation of immunological activity.¹¹

Learning/summary points

- most carcinoid tumours arise from the midgut. Of these the majority (appendiceal) are nearly always benign
- all tumours should be regarded as potentially malignant
- there is no firm clinical evidence linking long-term inhibition of gastric acid secretion with the development of gastric carcinoids
- urinary 5-HIAA is still the screening investigation of choice for suspected carcinoid syndrome, the hallmarks of which are flushing, diarrhoea, and wheezing
- the slow evolution of carcinoid tumours and their relatively good prognosis requires prolonged follow-up and relatively aggressive palliative intervention
- surgery and long-acting somatostatin analogues such as octreotide are the mainstays of treatment of metastatic carcinoid tumours and carcinoid syndrome
- chemotherapy has limited value as a second line treatment, and the benefits of interferons are reduced by side-effects
- somatostatin analogues with different receptor subtype specificities, as well as radiolabelled analogues, are being evaluated for future therapeutic use

Box 7

Main effects Octreotide potently inhibits the release of multiple gastroenteropancreatic and pituitary peptides/hormones by binding to tissue receptors. Other effects include inhibition of gallbladder contraction, acceleration of gastric emptying, prolongation of intestinal transit time, and increasing fluid/electrolyte absorption from gut. The latter underlie its mostly gastrointestinal side-effects (anorexia, nausea, vomiting, steatorrhoea, impaired glucose tolerance) which occur in about 30% of patients, usually temporarily. Gallstones, nearly always asymptomatic, develop in approximately 20% of patients treated for more than a month.³⁰

Clinical pharmacology Octreotide is usually administered thrice daily by subcutaneous injection. Typically, the maximum total daily dose is 1500 µg, although doses as high as 6000 µg/day have been used without serious problems. As mentioned, dose escalation is usually required eventually. Circulating octreotide is 65% protein bound and levels peak 30 and four minutes after subcutaneous and intravenous injection, respectively; 30–40% is metabolized in the liver and the dosage may need to be reduced in moderate to severe renal impairment.³¹ The annual cost for a total daily dose of 500 µg is currently £10 500.

Carcinoid crisis This is the development of profound hypotension (or occasionally hypertension), with or without bronchospasm, during induction of anaesthesia, initiation of chemotherapy, or tumour manipulation (including fine needle biopsy and embolisation). It is thought to occur because of the release of bioactive agents from the tumour, presumed largely secondary to the effects of stress-associated endogenous catecholamine release. Octreotide may be used very effectively as prophylaxis (100–400 µg subcutaneously pre-, intra-, and post-procedure), or to abort an established crisis (50–100 µg intravenously).⁷ Use of sympathomimetic vasoconstrictors is contraindicated during resuscitation since they are likely to aggravate an established crisis.³²

Newer somatostatin analogues

Although octreotide has considerable pharmacological advantages over the native peptide (eg, elimination half-life of 113 *vs* 3 min), there is room for improvement. The current need for thrice daily administration of octreotide is a particular practical problem. Clinical trials are underway with a microsphere-encapsulated slow-release formulation of a newer analogue called lanreotide (synonyms: BIM23014, somatuline, and angiopeptin). Like another agent, vapreotide (RC-160), it is relatively specific for sst 2 and 5, and to a lesser extent sst 4 receptor subtypes. Its plasma half-life (four to five days), and sustained reduction of plasma insulin-like growth factor-1, suggest that it could be given as infrequently as once every 10–14 days, by intramuscular injection.³³ A similar formulation of octreotide has successfully been given monthly for the treatment of acromegaly. Another obvious future goal is the development and trial of selective analogues for sst receptor subtypes 1, 3, and 4 for octreotide-insensitive tumours. Such agents are already becoming available.

Chemotherapy

In general, cytotoxic drugs are therapeutically disappointing whether given singly or in combination, systemically or regionally. With regard to malignant carcinoid tumours, responses are generally short-lived, and median survival times compare poorly to octreotide and interferons (7–12 *vs* 36 and 80 months, respectively).³⁴ The most frequently used agents are streptozotocin, and 5-fluorouracil; dacarbazine, doxorubicin, cyclophosphamide, and methotrexate have also been tried with little success. Multicentre randomised trials of streptozotocin-containing combinations have at best demonstrated response rates for metastatic carcinoids of 22–33%.³⁵ Chemotherapy alone does not appreciably improve survival and should probably be reserved for cases in which there is rapid tumour growth and/or failure to control symptoms by other means.³⁶

Interferons

Interferons are reported subjectively to improve diarrhoea, flushing, and bronchoconstriction in about two-thirds of patients. Used for periods of up to 30 months, human leukocyte interferon α is also reported to halve tumour size in 15% of patients, and curtail growth in another 39%. This contrasts with octreotide therapy in which a major drawback is the lack of effective and sustained tumour shrinkage. The median duration of response to interferons is quoted as 34 months (range 3–76). Prior chemotherapy is associated with reduced survival time (64 *vs* 80 months) in patients treated with interferon.³⁶

The main adverse effects of interferons are flu-like symptoms, constitutional upset, and haematological abnormalities. These can be transitory or may be manageable by dose reduction, but are greatly disliked by patients. Long-term use of interferon α -2b is associated with the development of auto-antibodies; neutralising interferon antibodies appear in 5–15% of patients and are correlated with treatment failure. The inducibility, in sample tumour cells, of an enzyme (2',5'-oligoadenylate synthetase) implicated in the antiviral and antimetabolic actions of interferons can be used to predict response to therapy and thus in patient selection.³⁷

Other treatments

Most symptomatic treatments have been superseded by octreotide, but obviously retain a role when this expensive drug is unavailable. Combined histamine H_1 and H_2 receptor blockade can effectively treat flushing and diarrhoea due to foregut carcinoids. Other drugs previously used to control flushing include kallikrein inhibitors and α -adrenergic blocking agents. In addition to codeine and loperamide, antagonists of 5-HT₁ (eg, methysergide) and 5-HT₂ receptors (eg, ketanserin) are well-established and effective anti-diarrhoeal agents; cyproheptadine is also worth trying. ICS 205-930, a 5-HT_{3/4} receptor antagonist is of limited clinical value and data concerning ondansetron are sparse. Conventional anti-asthma treatment may help bronchoconstriction. Niacin supplementation is less frequently needed for treatment of secondary pellagra.

Prognosis

As with other tumours, the size, and primary site (and to a lesser extent, histological growth pattern) of carcinoids is predictive of their natural history. As might be expected, the development of carcinoid syndrome carries a poor prognosis. An ectopic endocrine syndrome is predictive of malignancy.³⁸

As noted, limited evidence suggests octreotide²⁷ and interferons may improve survival.³⁴ Survival figures in the literature are often based on studies that predate the advent of octreotide. Frequently quoted is the large analysis (1867 patients) of cancer registry data published by Godwin in 1975,¹ whose figures are broadly representative of other smaller series. For localized tumours, the median five-year survival was 92–99% for all sites except the small intestine/ileocaecum (75%) and colon (77%). Corresponding information for tumours of all stages was as follows: appendix 99%, stomach, small intestine and ileocaecum, and colon each >50%, and other sites >80%. Mean survival after the first flushing episode and six-year survival was 36 months and 25%, respectively.

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