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Review

Chemotherapy for the Carcinoid Syndrome

Adrian L. Harris

Royal Marsden Hospital,
Fulham Road, London SW3, Great Britain

Summary. *Patients with carcinoid syndrome usually die from carcinomatosis, rather than the pharmacological effects of the tumour. Functioning carcinoid tumours are resistant to radiotherapy. Twenty-four different cytotoxic drugs or combinations have been used to treat the carcinoid syndrome, but only actinomycin D, cyclophosphamide, 5-fluorouracil, melphalan, methotrexate, and streptozotocin have been tried as single agents in more than five patients. 5-Fluorouracil and streptozotocin were the most effective single agents, but their use in combination did not increase response rates. No drug combination was superior to single-agent therapy. Adriamycin has not been tested as a single agent, but results with it used in combination suggest it should be further evaluated. Liposome-encapsulated drugs may be tested, because of selective hepatic uptake.*

Introduction

Natural History

Functioning carcinoid tumours are rare (0.05%–0.2% of all neoplasms) [37], and therefore relatively little experience is individually gained in their management. The general impression is that they are slow-growing tumours, the major problems being flushing, wheezing, diarrhoea, and cardiac lesions. A study of the largest individual series of functioning carcinoid tumours [14] shows that there is a 50% mortality at 3 years from the onset of flushing and 75% at 6 years. About 15% survive 10 years, and so some patients have stable disease with no therapeutic intervention. The tumour affects a younger population than most other gastrointestinal carcinomas [4].

Approximately 75% of carcinoid tumours associated with the carcinoid syndrome arise in the small bowel [14, 16], although only 10% of small-intestinal carcinoids are associated with the syndrome and these have nodal or hepatic secondary deposits.

Attempts a Therapy

1. Pharmacological Therapy

Flushing, wheezing, and hypotension are poorly controlled with current antiserotonin therapy [26] although pharmacological attempts to control the syndrome are the first line of approach. Five main groups of drugs have been used [1, 14, 26, 35, 38, 65, 67]. Only the diarrhoea is readily controlled by pharmacological therapy – usually by opiates or serotonin antagonists.

Antiserotonin Compounds. Antiserotonin compounds may produce relief of diarrhoea but usually do not help flushing. Cyproheptadine may control both, and produces a sense of well-being. Methysergide and parachlorophenylalanine have been effective in controlling diarrhoea. α-Methyldopa usually makes patients feel worse.

Phenothiazines. Chlorpromazine has been effective in relieving flushing, and may also improve appetite.

Corticosteroids. Prednisolone is particularly useful in suppressing the flushing associated with bronchial carcinoids, but not with small-intestinal tumours.

α-Blockers. Because catecholamine release with stress or exercise may cause release of kinins, one of the mediators of the carcinoid syndrome, α-blockers have been tried. Phenoxybenzamine and phentolamine may prevent flushing, but produce hypotension. β-Blockers are not effective.

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Aprotonin. The kallikrein-bradykinin inhibitor aprotonin (Trasylol) has been given to prevent carcinoid crisis after tumour embolisation, but it does not prevent flushing. In one patient bronchospasm and hypotension during anaesthesia were reversed.

Recently somatostatin infusions have been shown to inhibit flushing, diarrhoea and hypotension [12, 20]. However, since they mainly prevent release of the mediators of the carcinoid syndrome, severe rebound flushing and hypotension occurred when the infusions were discontinued. A longer-acting analogue is now available, but long-term use has not been reported [32].

Cardiac lesions may not be caused by serotonin, are found in 75% of patients at post-mortem and are a common cause of mortality [37]. Most deaths seem to be due to carcinomatosis per se [14], and carcinoid tumour growth is not controlled by blocking agents.

2. *Radiotherapy*

The carcinoid tumour is reportedly radioresistant and although good responses have been obtained with current high-voltage radiotherapy (Co^{60}, 2,500 rad/5 weeks) none of the functioning tumours responded [21, 49, 63]. A similar lack of response in functioning and non-functioning tumours has been recorded by others [3, 8, 29, 50, 51, 57]. This may be because 5-HT is radioprotective [4, 15, 60].

3. *Surgery*

The direct surgical removal of liver secondaries or mesenteric and omental nodes may produce great relief of symptoms [41]. Surgical removal of operable secondaries is probably the treatment of choice [58, 61, 68]. However, many patients do not have single liver secondaries amenable to surgery; anaesthesia may produce a fatal crisis before any direct handling of the tumour occurs [35, 57]; and postoperative complications are relatively frequent [35, 64].

Recently devascularisation of hepatic secondaries by ligation or embolisation of the hepatic artery has produced good therapeutic results [1, 16, 34, 43] but it is not always effective [16]. It may result initially in worsening of the symptoms [43], and death has occurred within a few hours or days of hepatic artery ligation [11, 17]. The patients with the most severe symptoms or cardiac problems may be the least able to tolerate this approach.

None of the above forms of treatment is of help to patients with extensive abdominal spread of tumour. Patients with symptomatic local and distant metastatic disease, and with hepatic secondaries not suitable for resection, could be considered for treatment with cytotoxic chemotherapy. The literature on single and combination chemotherapy in the malignant carcinoid syndrome has been reviewed to decide which drugs should be further evaluated for treatment of these patients.

Chemotherapy

Problems arise in the review of the literature on chemotherapy. Many authors have included patients with non-functioning carcinoid tumours in their series [8, 31, 34, 46]. These patients do not present the same clinical problems, apart from local and metastatic disease. They may be more radiosensitive (see Introduction) and have longer survival than those with functioning carcinoids. The 5-year survival for non-functioning carcinoid tumour of the small intestine with nodal or hepatic secondaries is about 50% [6, 23, 30], nearly double that for functioning tumours. Where possible the data for those with carcinoid syndrome have therefore been extracted from the series reviewed.

The initial indications for chemotherapy are often not documented and responses have been categorised in different ways. Thus 'stable disease' has been counted as a response [31] when really what is meant is no change in response to the drugs. Responses have been classified as 'objective' when liver size decreases or urine 5HIAA falls, but often this is not accompanied by symptomatic improvement [35, 36]. Since the main reason for treating the majority of patients is symptoms of the carcinoid syndrome, symptomatic (subjective) response is most important. Both objective and subjective responses are shown in the tables where the authors have included the information. Stable disease is equated with no response.

Some authors have expressed response rates to individual courses of the same chemotherapy, so that some patients would be counted twice [33, 36]. In this review such patients are counted only once.

Single Agents

From Table 1 it can be seen that very few drugs have been used in more than five patients. The two drugs that seem most effective in relieving symptoms as well as producing objective changes are 5-FU and streptozotocin. There seems little to choose between them in terms of efficacy, although streptozotocin had more severe side effects, particularly nephrotoxicity and nausea.

Table 1. Single agents used in more than five patients with malignant carcinoid syndrome

Drugs	No. of patients (total)	Response			Ref.
		Obj. (%)	Subj. (%)	Stable or none	
Actinomycin D	9	1	–	8	[39]
Cyclophosphamide	6	4	0	2	[35]
	8[a]	–	–	8	[40]
	1	1	1	–	[67]
	(15)	(33)	(7)		
5 FU	15	6[b]	6	9	[39]
	1	1	1	–	[47]
	1	1	1	–	[46]
	1	1	1	–	[46]
	11[a]	2	–	9	[40]
	1	–	–	1	[13]
	(30)	(36)	(30)		
Melphalan	8	5	0	3	[33]
	6	–	–	6	[39]
	(14)	(36)	(0)		
Methrotrexate	6	3	0	3	[36]
Streptozotocin	6	3	–	3	[39]
	4[c]	2	4	1	[42]
	2	2	2	–	[27]
	4[a]	–	–	4	[52]
	4[a]	1	2	2	[59]
	2	2	2	–	[18]
	(18)	(44)	(50)		

[a] Series include patients with non-functioning carcinoid tumours
[b] One patient had no change in urine 5HIAA
[c] These are probably included in Ref. 39

Table 2. Drugs used in five or fewer patients with the malignant carcinoid syndrome

Drug	No. of patients	Response			Ref.
		Obj.	Subj.	Stable or none	
BCNU	1	–	–	1	[39]
Chlorambucil	1	1	1	–	[62]
DTIC	1	–	–	1	[39]
	2	1	2	–	[27]
Fluoromethalone	5	–	–	5	
Hydroxyurea	1	–	–	–	[39]
Mitomycin C	3	–	–	3	
	Not stated	Yes	Yes		[55]
5 FU by hepatic artery perfusion	1	1	1	–	[46]
	2[a]	2	2	–	[43]
	2	–	–	2[b]	[17]
Nitrogen mustard	1	1	1	–	[65]

[a] Included non-functioning carcinoid
[b] 1 patient died within 4 days

The other single agents that have produced objective responses are cyclophosphamide and melphalan (Table 1). However there was no improvement in symptoms.

None of the drugs used in fewer than five patients (Table 2) looks particularly encouraging, although the numbers are too small for valid conclusions. DTIC and chlorambucil have produced good subjective and objective responses.

5-Fluorouracil has been given by hepatic artery perfusion, but "it is clearly not possible to assess the independent effect of the cytotoxic therapy and hepatic artery ligation in many of these patients" [43]. Furthermore, this mode of administration has not been shown to produce a higher reponse rate than 5-FU given systemically in an optimum manner [2], and local complications may be severe [46].

Combinations

5-Fluorouracil and streptozotocin can be used at their individual maximum doses in combination because their side-effects are different. Although preliminary results looked encouraging [39], a large-scale study including patients with non-functioning carcinoid showed no improvement in response rates [40]. Others have also found this [7].

A wide range of combinations have been used in small numbers of patients (Table 3). Of particular interest are the results from the MD Anderson Hospital [31]. Thirty-two carcinoid patients were treated with a variety of drugs, although only 12 had the carcinoid syndrome. Only seven patients in the series responded to chemotherapy. Of the seven, five responded to regimens containing adriamycin. Adriamycin alone does not seem to have been used in the carcinoid syndrome, although it has been used in one patient with a malignant carcinoid tumour, with good response [48]. In one patient with the carcinoid syndrome [56] adriamycin seemed to be the active component of a combination including cyclophosphamide and methotrexate.

Medullary carcinoma of the thyroid and carcinoid tumours have embryological, ultrastructural and histological characteristics in common [45]. Diarrhoea is also associated with medullary carcinoma of the thyroid. Adriamycin produced partial remission in three of four patients with medullary [24] carcinoma of the thyroid, a type usually refractory to therapy. One patient with diarrhoea had complete relief of his symptoms with no change in tumour bulk. This is similar to observations that have been made in the carcinoid syndrome [27].

Table 3. Combination chemotherapy for the malignant carcinoid syndrome

Drugs	No. of patients (total)	Response			Ref.
		Obj. (%)	Subj. (%)	Stable or none	
Streptozotocin + 5 FU	44[a]	14	–	–	[40]
	5	4	4	1	[16]
	10[a]	4[b]	–	8	[7]
	1	1	–	–	[53]
	9	6[c]	–	–	[39]
	(69)	(42)			
5 FU + BCNU	1	–	–	1	[39]
Streptozotocin + BCNU	1	1	–	–	[39]
Methotrexate + cyclophosphamide	4	3	0	1	[36]
Methotrexate + cyclophosphamide + adriamycin	1	1	–	–	[54]
	1	1	1	–	[56]
Cyclophosphamide + streptozotocin	45[a]	12	–	–	[40]
Ftorafur + BCNU + adriamycin	2[a]	1	–	1	[31]
Adriamycin + 5 FU	3[a]	2	–	1	
Adriamycin – DNA complex	3[a]	2	–	–	
5 FUdR + ara-C	1	1	–	–	[10]

[a] Series include patients without carcinoid syndrome
[b] Two patients had carcinoid syndrome and fall in 5HIAA
[c] Three patients showed no change in urine 5HIAA

Radioisotopes

Radioactive colloidal gold ^{198}Au, which is mainly taken up in the liver, produced good objective and subjective responses in three patients [22, 57].

Complications of Chemotherapy

Second Tumours

The effective chemotherapy of the carcinoid syndrome may be expected to prolong survival. In several previously fatal neoplasms (Hodgkin's disease, multiple myeloma, and cancer of the ovary) prolonged survival after chemotherapy has been associated with an increased incidence of second neoplasms. However, carcinoid tumours themselves are associated with a higher incidence of second neoplasms, ranging from 17% of a large series [41] to 53% of smaller series [19, 23, 30, 44, 66]. A later series of patients with carcinoid syndrome had a lower incidence of 5.5% [14].

Carcinoid Crisis

Exacerbations of the syndrome commonly occur following chemotherapy. Some patients may develop severe continuous flushing, tachycardia and hypotension. Two fatal cases have been reported [5, 34]. Antagonists of 5-HT are not effective, and addition of steroids, fluid replacement, metaramine, and angiotensin failed to produce improvement.

To prevent this complication, Trasylol, cyproheptadine and parachlorophenylalanine were given to two patients prior to embolisation [1]. No exacerbation occurred, but hepatic artery ligation has been well tolerated without these drugs [43]. Two of 64 patients studied by the Eastern Cooperative Oncology Group developed carcinoid crisis after chemotherapy [5].

Adequate hydration is important in these patients and can produce improvement in symptoms without any specific therapy [35]. Haemodialysis has been suggested [9].

Conclusions

1. Massive tumour cell necrosis should be avoided because of the risk of carcinoid crisis. However, in the post-mortem of one patient [5] tumour cell necrosis was not extensive.
2. It is not possible to conclude that the mode of action of chemotherapy is to reduce tumour bulk and hence the amount of endogenous mediators produced.

Patients may have exacerbations of symptoms with no improvement subjectively or objectively [36, 38].

Others can have objective responses with decrease in liver size and urine 5HIAA, with no improvement in symptoms [36].

Some patients have decrease in liver size, decrease in symptoms, but no change in urine 5HIAA [39].

Patients may also improve symptomatically with no change in liver scan or urine 5HIAA [27].

3. The best single agent is 5-FU.
4. Most drugs have not been adequately assessed on their own.
5. Response rates to combinations do not seem higher than to single agents.

Suggestions for Chemotherapy

1. Use single agent first – 5-FU.
2. Adriamycin, although not tested on its own, looks the most promising established drug to try.
3. Liposomes are accumulated in the liver in man [28] and liposome-encapsulated drugs could be tried [25] in view of the good responses to colloidal gold ^{198}Au.
4. Phase II studies of new agents are warranted in view of poor response rates to most standard drugs.

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