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ORIGINAL ARTICLE

Phase II study of thalidomide in patients with metastatic carcinoid and islet cell tumors

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Abstract
Purpose Carcinoid and islet cell tumors are known to be highly vascular. There is no effective systemic therapy currently available for metastatic disease. We conducted a phase II trial to evaluate the efficacy of the anti-antiangiogenic agent thalidomide in metastatic neuroendocrine tumors.
Patients and methods Eighteen patients with measurable, histologically proven metastatic carcinoid neuroendocrine carcinomas (well-differentiated, $n = 13$; moderately-differentiated, $n = 5$) were enrolled on this study. The majority of the patients had gastrointestinal primaries (small bowel, 8; pancreas, 5; colon, 1). All but one patient had hepatic metastases, and 12 patients (67%) had carcinoid syndrome. All patients had Eastern Cooperative Oncology Group performance status of zero or one. Eight patients (44%) had received previous hepatic artery chemoembolization and 11 (61%) had undergone surgical resection. Patients were started on oral thalidomide at a daily dose of 200 mg that was escalated to the target dose of 400 mg daily after 2 weeks. Tumor response was assessed at 12-week intervals using RECIST criteria. Planned treatment duration was 24 weeks unless unacceptable toxicity or disease progression was observed.
Results No patient achieved a partial remission or a complete remission. Best response was stable disease (SD) in 11 of 16 response-evaluable patients (69%). Serum pancreastatin results did not correlate with clinical response. Grade 3 toxicities included dizziness with orthostatic hypotension ($n = 5$), sensory neuropathy ($n = 2$), fatigue ($n = 2$), hemorrhagic cystitis ($n = 1$), and deep venous thrombosis ($n = 1$). Frequent Grade 1–2 toxicities were: fatigue ($n = 13$), constipation ($n = 13$), dry mouth ($n = 12$), somnolence ($n = 12$), dizziness/syncope ($n = 10$), weight gain ($n = 5$), and peripheral neuropathy (n = 5).
Conclusions Thalidomide was fairly well tolerated in patients with metastatic carcinoid/islet cell tumors, but failed to reveal any objective responses. The single stage design of the trial makes it difficult to determine whether observed SD in a subset of patients was attributable to the indolent nature of these tumors, or to beneficial effect of thalidomide.

Keywords Carcinoid tumor · Islet cell tumor · Anti-angiogenic therapy · Thalidomide · Phase II trial

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Introduction

Carcinoid and islet cell neuroendocrine tumors are characterized by hypervascularity and an indolent growth pattern [25]. It is now believed that the increasing tendency for aggressive local invasive behavior and distant metastasis is associated with histological differentiation [15]. Neuroendocrine tumors typically produce various biogenic amine products that can be quantitated in tumor cells as well as in the serum. Clinically, the tumors are often associated with hormone-related symptoms of flushing and diarrhea, defined as carcinoid syndrome [24].

Aggressive surgical resection is recommended as initial treatment for well- and moderately-differentiated tumors. Octreotide or its long-acting analogue is effective in controlling the hormone-related symptoms [26]. No systemic

therapy has been found to consistently elicit tumor response or prolong survival for patients with metastatic neuroendocrine tumors. Systemic chemotherapy using 5-fluoruracil, doxorubicin, and streptozotocin alone or in combination has poor disease control rates, demonstrating 10–20% objective response in metastatic carcinoid tumors, and 40–70% in metastatic islet cell tumors [18]. Hepatic artery chemoembolization (HACE) produces palliation of symptoms and biochemical response in 50–100% of patients, with median response duration of 14–29 months [6]. Interferon-alpha used alone or in combination with octreotide is associated with a 25% response rate [4]. Newer agents currently under investigation for the management of neuroendocrine tumor metastatic to the liver include radiolabeled octreotide, the anti-angiogenic agents bevacizumab and SU11248, and the epidermal growth factor receptor-small molecule inhibitor gefitinib.

Thalidomide is a non-barbiturate sedative and hypnotic drug that has subsequently been found to have anti-angiogenic and immunomodulatory properties [2, 13]. Immunomodulatory mechanisms include inhibition of TNF-α synthesis by activated macrophages and co-stimulation of T cells that have been partially activated by the T-cell receptor [2]. Because of its anti-angiogenic properties, thalidomide has been investigated as an anti-neoplastic agent [2], and has demonstrated activity in up to 30% of patients with refractory multiple myeloma [24]. Encouraging results were also reported in initial studies of thalidomide for the treatment of various solid tumors, including AIDS-related Kaposi sarcoma, melanoma, and renal cell carcinoma, all of which are known to be highly vascular [10, 14, 19]. We hypothesized that thalidomide would demonstrate activity against carcinoid and islet cell tumors.

The primary objective of this trial was to assess the objective response rate in patients with well- or moderately-differentiated neuroendocrine carcinoma treated with low dose single agent thalidomide. Secondary objectives were to assess toxicity, and to measure the levels of serum tumor markers such as pancreastatin.

Patients and methods

Eligibility criteria

A phase II trial of thalidomide for patients with metastatic neuroendocrine tumors was conducted at the Ohio State University Comprehensive Cancer Center (OSU CCC), following approval by the OSU Institutional Review Board (Protocol #00H0382). Eligibility criteria included histologically confirmed, metastatic, well- or moderately-differentiated neuroendocrine carcinoma, age ≥18, life expectancy of at least 6 months, Eastern Cooperative Oncology Group performance status of 0–2, and adequate organ function (total bilirubin <1.5 mg/dl, AST and ALT < 2.5 x upper limit of normal, absolute neutrophil count >1,500/μl, and platelet count >100,000/μl). Patients were required to have measurable disease. Those patients who had undergone previous HACE were required to have either progression of the hepatic lesions at least 12 weeks post treatment, or to have measurable extrahepatic disease. Patients were allowed one previous systemic chemotherapy regimen. Prior radiation therapy or immunotherapy was allowed if at least 4 weeks had passed since treatment. Patients were allowed maintenance therapy with long-acting octreotide (Sandostatin LAR, Novartis Pharmaceuticals Co., East Hanover, NJ) for control of carcinoid symptoms, provided that the dose was stable for 3 months prior to study entry. Due to the known teratogenicity of thalidomide, all patients were required to enroll in the S.T.E.P.S.® (System for Thalidomide Education and Prescribing Safety) program and to abide by the birth control and pregnancy testing requirements of the S.T.E.P.S.® program. Serum β-human chorionic gonadotropin was obtained within 24 h before initiation of therapy, weekly during the first month, and every 2 or 4 weeks thereafter depending on regularity of menstruation for all female patients of childbearing potential. Pregnancy, lactation, and uncontrolled intercurrent illness were absolute contraindications to trial entry. Each patient gave informed consent to participate in the trial.

Study design

Thalidomide (Celgene Corporation, Summit, NJ) was initiated at a daily oral dose of 200 mg/day, increased to 300 mg/day after the first week, and increased again to the target dose of 400 mg/day after the second week. Laxatives and stool softeners were used on a prophylactic basis in all patients except those having tumor-related diarrhea. Toxicity was assessed using the Common Toxicity Criteria version 2.0. Grade 2 peripheral neuropathy was managed by treatment delay until resolution to Grade 1. Grade 3 constipation or somnolence were managed by treatment delay until resolution to Grade 2. Thalidomide was restarted at 100 mg/day and then increased at 100 mg increments every 3–7 days as tolerated to a maximum dose of 400 mg/day. A minimum daily dose of 100 mg was permitted. If an exfoliative, purpuric, or bullous skin rash developed, or if Stevens–Johnson syndrome or toxic epidermal necrolysis was suspected, patients were removed from study. Therapy was administered for a total of 24 weeks or until patients developed progressive disease (PD), had treatment held for more than 4 weeks, developed a Grade 4 adverse event, or withdrew from the study. The end point of 24 weeks was chosen in order to minimize the likelihood of developing cumulative side

effects related to thalidomide treatment that might be irreversible, in the setting of lack of clear benefit related to thalidomide therapy. Secondly, carcinoid tumors are relatively slow-growing, and patients in this study were not required to have progressive disease at study entry. Under such circumstances, stable disease (SD) of duration up to several months or years may not necessarily be attributable to the study drug. Thus, a predetermined length of maximum study duration was utilized if patients did not have evidence of objective response.

History, physical examination, complete blood count, and serum chemistry were done within 14 days prior to initiation, every 4 weeks while on study, and within 4 weeks after the last dose of thalidomide. Prior to enrollment, patients underwent CT scans of the chest, abdomen and pelvis, and other sites as appropriate. Patients were restaged after 12 weeks, and those exhibiting PD were removed from the trial. Patients exhibiting a clinical response or SD by RECIST criteria were permitted to continue therapy for an additional 12 weeks. Staging was repeated at the off-study visit.

Measurement of tumor markers

Within 14 days prior to initiation of therapy, tumor markers [serum pancreastatin, vasoactive intestinal polypeptide (VIP), gastrin releasing peptide (GRP), neurotensin, pancreatic polypeptide (PP), substance P, calcitonin, gastrin, glucagon; and 24 h urinary 5-hydroxy indole acetic acid] were obtained. Pancreastatin was chosen instead of chromogranin-A because the pancreastatin assay is routinely performed in the clinical laboratory at our center. Pancreastatin is a split-product of chromogranin-A that has good prognostic value. Measurement of tumor markers was performed every 12 weeks on study and at the off-study visit.

Measurement of gene expression of angiogenic and immunologic markers by real-time reverse transcription-PCR

Peripheral blood was obtained from patients at various time points. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation (Ficoll-Paque, Amersham Pharmacia Biotech, Uppsala, Sweden). Real-time reverse transcription (RT)-PCR was performed as detailed previously [9]. Briefly, total RNA was isolated using the RNAqueous isolation kit (Ambion, Austin, TX) and cDNAs were generated by RT of 1–2 μg of cellular RNA in the presence of random hexamer primers (Clontech, Palo Alto, CA) following the manufacturer's recommendations. Each cDNA sample (2.5 μl) was then used as a template for a PCR amplification mixture utilizing 2X Taqman Universal PCR Master Mix (PE Applied Biosystems, Foster City, CA). Reaction mixtures were subjected to the following scheme: 1 cycle at 50°C for 2 min, 1 cycle at 95°C for10 min, followed by 40 cycles at 95°C for 15 s and 60°C for 1 min. Forward and reverse primers for human 18S rRNA, a housekeeping gene, were used as an internal control in each reaction well.

Statistical methods

This study was a phase II trial employing a Simon minimax two-stage design. Thalidomide was to be considered ineffective if the true response probability P_0 was less than 10%. The regimen would be deemed worthy of further study if the true response probability of target response rate P_1 was 30% or greater. These figures resulted in a two-stage design of 16 and 25 patients, with an alpha of 0.10 and beta of 0.10. If zero or one response was observed in the first 16 response-evaluable patients, the study would be terminated early. If two or more patients responded in the initial 16, an additional 9 patients would be treated, for a total of 25 patients.

Results

Patients

Between April 2001 and July 2001, a total of 18 patients (9 male, 9 female) were accrued to the trial, in order to obtain 16 response-evaluable patients in the first stage of the trial. Clinical characteristics of the patients are presented in Table 1. The median age was 55 (range 38–78). Thirteen patients (72%) had well-differentiated tumors. The site of primary tumor was carcinoid in 13 patients, and islet cell tumor in 5 patients. The majority of patients had both hepatic and intra-abdominal lymph node metastases (10 patients, 56%). Two-thirds of the patients had carcinoid syndrome. Most of the patients had undergone surgical resection, and 8 patients (44%) had previously undergone HACE.

Treatment administered

If the best response achieved was SD, treatment with thalidomide was continued for a maximum of 24 weeks. The median duration of therapy for all 18 patients was 24 weeks (range, 1–24), and 11 of 18 patients (61%) completed 24 weeks of therapy. The reasons for treatment cessation prior to the 24 weeks of planned therapy included PD ($n = 3$), grade 3 neuropathy ($n = 2$), grade 3 dizziness ($n = 1$), and patient withdrawal at one week due to grade 2 dizziness, headache, and imbalance ($n = 1$).

Table 1 Patient characteristics

Characteristic	Number	Percent
Total patients	18	100
Age (years)		
Median	55	
Range	38–78	
Gender		
Male	9	50
Female	9	50
ECOG performance status		
0–1	18	100
Histologic grade		
Well-differentiated	13	72
Moderately-differentiated	5	28
Site of primary tumor		
Carcinoid	13	72
Small bowel	8	44
Colon	1	6
Unknown	4	22
Pancreatic islet cell tumor	5	28
Site of metastasis		
Liver alone	6	34
Liver and abdominal lymph nodes	10	56
Liver and bone	1	5
Peritoneal implants	1	5
Carcinoid syndrome/octreotide therapy		
Present	12	67
Absent	6	33
Prior treatment		
Debulking or palliative surgery	11	61
Hepatic artery chemoembolization	8	44
Systemic chemotherapy	3	16
Elevation of serum tumor markers at baseline		
Pancreastatin	18	100
Glucagon	10	63
Pancreatic polypeptide	5	29
Substance P	3	18
Gastrin	3	18
Neurotensin	2	12
Elevation of Urinary 5-HIAA[a] at baseline		
Present	8	44
Absent	10	56

[a] 5-HIAA, 5-hydroxyindole acetic acid

Response to therapy

Outcome data is summarized in Table 2. Two of the 18 patients enrolled went off study prior to the week 12 response evaluation; thus, 16 patients were evaluable for response. No patients achieved a partial remission (PR) or a complete remission (CR). Best response of SD was observed in 11 of 16 patients (69%). Five patients (31%) had PD. Subgroup analysis of patient response is presented in Table 2. Of the 11 patients who terminated study participation at 24 weeks, 2 had progressive disease at the time of study termination. Nine patients had SD at the time of study termination. Of these, one developed chronic renal failure on thalidomide and died 15 months later. One patient was discovered to have head and neck cancer after study termination; however, at last follow-up (62 months), the endocrine disease was stable. The other 7 of the 9 patients developed disease progression (median 7 months) after study termination. Interestingly, of five patients who had evidence of disease progression in the 6 months prior to enrollment in the trial, 3 achieved SD during treatment with thalidomide, and then once again exhibited PD after discontinuation of thalidomide.

Table 2 Treatment outcome

Type of response or tumor (n = total number of patients)	SD number (%)	PD number (%)
Best response (n = 16)	11 (69)	5 (31)
Well-differentiated neuroendocrine CA (n = 11)	9 (82)	2 (18)
Moderately-differentiated neuroendocrine CA (n = 5)	2 (40)	3 (60)
Carcinoid tumor (n = 12)	9 (75)	3 (25)
Islet cell tumor (n = 4)	2 (50)	2 (50)

Adverse events

Adverse events (AEs) are summarized in Table 3. In general, oral thalidomide was reasonably well-tolerated. No grade 4 or 5 AEs were encountered. Four patients stopped treatment due to toxicity. One patient had grade 2 headache and dizziness and elected to stop therapy after one week. A total of 5 patients developed grade 3 dizziness while on thalidomide. Three patients developed grade 3 dizziness at 4, 8, and 16 weeks. Two of these patients responded to dose reduction to 100 mg daily with reversion to grade 1 dizziness, and the third patient experienced resolution after discontinuation of thalidomide for 4 days and was able to resume therapy at the full dose. All three of these patients remained on study for the full 24 weeks. One patient developed grade 3 dizziness, grade 2 facial numbness, and rash at 5 weeks and was taken off study. One patient developed grade 3 dizziness at 4 weeks that responded to dose reduction to 100 mg daily, but subsequently developed grade 3 motor neuropathy and was

Table 3 Adverse events

Adverse event	Grade 1 number (%)	Grade 2 number (%)	Grade 3 number (%)
Dry mouth	12 (67)	0	0
Fatigue	12 (67)	1(6)	2 (11)
Somnolence	11 (61)	1 (6)	0
Weight gain	5 (28)	0	0
Constipation	4 (22)	9 (50)	0
Dizziness/syncope	7 (39)	3 (17)	5 (28)
Ataxia	1 (6)	1 (6)	0
Tremor	1 (6)	0	0
Neuropathy (sensory)	2 (11)	2 (11)	2 (11)
Neuropathy (motor)	1 (6)	0	0
Headache	1 (6)	2 (11)	0
Hemorrhagic cystitis	0	0	1 (6)
Skin rash	3 (17)	0	0
Deep vein thrombosis	0	0	1 (6)

taken off study at 20 weeks. A second patient developed grade 3 neuropathy and was taken off study at 16 weeks. Common grade 1–2 toxicities observed were expected and were of constitutional, gastrointestinal and neurologic nature (Table 3). Infrequent toxicities included hemorrhagic cystitis (1), tremor (1), rash (1), deep vein thrombosis (1), and severe headache (1). The majority of the patients (15) maintained performance status of 0–1 throughout the study.

Tumor markers

The levels of common neuroendocrine tumor markers were evaluated at baseline and at 12 and 24 weeks. While the baseline serum pancreastatin level was elevated in all 18 patients, baseline levels of other neuroendocrine tumor markers varied among patients (Table 1). Among the 12 patients with carcinoid tumors, elevated pancreastatin was the only detected serum tumor marker in 3 patients. Serum pancreastatin levels either remained stable or increased only slightly over time in all patients, and no observable difference in tumor marker levels was seen between patients with SD and those with PD (Table 4). We attempted to correlate serum pancreastatin levels with radiologic response. Serum tumor marker levels within 50% range variation of the baseline value were taken as a correlate for SD. For pancreastatin, 7 patients in the SD group showed rough correlation, while among the 5 patients in the PD group, none showed correlation (data not shown). Overall, the chance of correlation between pancreastatin levels and radiologic response was only 43% in this study.

Gene expression of angiogenic and immunologic markers

Of a total of 9 patients who had total RNA available to perform real-time RT-PCR, 5 patients had RNA available at the 12 week timepoint. Real-time RT-PCR for TNF-alpha, IL-1b, IL-6, and IFN-gamma (all cytokines known to be important in angiogenesis) in this small group of patients did not reveal any relationship between gene expression changes and clinical response (Table 5).

Discussion

Thalidomide (200 mg/day escalating to the target dose of 400 mg/day) was administered to 18 patients with measurable, histologically proven metastatic neuroendocrine carcinoma for up to 24 weeks. No clinical complete or partial responses were observed. Eleven of 16 response-evaluable patients (69%) had a best response of SD. Importantly, because of the indolent nature of the disease and the single stage trial design, the SD observed in our patients may not be due to thalidomide. Thalidomide was reasonably well tolerated. Five patients developed grade 3 dizziness with orthostatic hypotension. This responded to dose reduction in three patients, to a 4-day drug holiday in one patient, and resulted in removal from the study in one patient. Two patients developed grade 3 peripheral neuropathy necessitating drug discontinuation. Common grade 1–2 AEs included dry mouth, fatigue, somnolence, peripheral neuropathy, dizziness, and constipation. The observed toxicities in our study are consistent with those in other phase II trials of thalidomide for non-plasma cell malignancies.

As compared to the encouraging results observed in multiple myeloma and related plasma cell malignancies, the use of single-agent thalidomide for the treatment of advanced solid tumors, e.g. renal cell cancer, breast cancer, and head and neck cancer does not appear to be as effective [7, 19, 27]. Baidas et al. [1] reported on 28 patients with metastatic breast cancer. No partial or complete responses were observed, even at the dose level of 800 mg/day. Among a group of 26 patients with unresectable hepatocellular carcinoma treated with a median dose of 300 mg/day of thalidomide, one achieved a partial response and two had SD [17]. The best response rates for single-agent thalidomide in solid tumors have probably been in two recent trials, one for recurrent, high-grade glioma [11] and one for metastatic renal cell carcinoma [8]. Fine et al. [11] reported on 36 evaluable patients with recurrent high-grade glioma, of whom there were two radiographic partial responses, two minor responses, and 12 patients with SD. Similarly, Escudier et al. [8] reported 2 partial responses and 9 patients with SD of 6 months or more among 40 patients with progressive metastatic renal cell cancer. Of note, much higher

Table 4 Serum pancreastatin levels for patients on the study

Patient Identifier	Pancreastatin at baseline (pg/ml)	Pancreastatin at 12 week (% difference)[a]	Pancreastatin at 24 week (% difference)[a]	Clinical response
003	450	306 (−32)	493 (10)	SD at 24 week
005	1,860	4,080 (119)	3,760 (102)	SD at 24 week
007	1,020	1,980 (94)	N/A	SD at 24 week
008	1,080	1,410 (31)	1,150 (6)	SD at 24 week
010	15,500	13,500 (−13)	16,700 (8)	SD at 24 week
012	46,600	42,800 (−8)	34,500 (−26)	SD at 24 week
013	1,750	1,810 (3)	2,620 (50)	SD at 24 week
016	16,200	20,600 (27)	15,400 (−5)	SD at 24 week
017	847	501 (−41)	690 (−18)	SD at 24 week
001	1,670	1,780 (7)	2,580 (54)	PD at 24 week
014	1,170	1,150 (−2)	1,330 (14)	PD at 24 week
018	59,600	181,000 (204)	N/A	Off study at 20 week; SD
009	927	642 (−31)	595 (−36)	Off study at 16 week; SD
002	940	1,120 (19)	N/A	Off study at 12 week; PD
015	1,410	1,954 (39)	N/A	Off study at 12 week; PD
004	3,390	2,470 (−27)	N/A	Off study at 12 week; PD
011	672	N/A	N/A	Off study at 5 week
006	31,000	N/A	N/A	Off study at 1 week

N/A not available

[a] Percent difference calculated as compared to baseline value

Table 5 Gene expression of angiogenic/immunologic markers in PBMCs

Patient	TNF-alpha	IL-1b	IL-6	IFN-gamma	Clinical response
010	1.07	1.97	1.55	0.44	SD at 24 week
013	N/A	5.13	N/A	N/A	SD at 24 week
018	N/A	0.04	0.04	0.33	Off study at 20 week; SD
004	0.56	N/A	N/A	N/A	Off study at 12 week; PD
015	N/A	3.03	4.82	15.24	Off study at 12 week; PD

Fold change at 12 week as compared to baseline

doses of thalidomide were used than in many other studies (up to 1,200 mg/day), increasing the risk for development of major toxicities.

Recent studies have primarily evaluated thalidomide as part of combination therapies for solid tumors. Pujol et al. [21] evaluated 92 patients with SCLC responsive to initial chemotherapy. Patients were subsequently randomized to receive either chemotherapy (PCDE) plus thalidomide (400 mg daily) or chemotherapy plus placebo for 4 subsequent cycles. Median survival was 11.7 months for the thalidomide group and 8.7 months for the placebo group. Kulke et al. [16] evaluated 29 patients treated with temozolomide (150 mg/m^2 for 7 days every other week) plus thalidomide (50–400 mg daily, median administered dose 100 mg) for metastatic neuroendocrine tumor. There were six partial radiologic responses and one complete response. These results suggest that the best use for thalidomide is likely in combination regimens.

In this group of carcinoid tumor and pancreatic islet cell tumors, the best clinical response was SD in 69% of patients. Because of the indolent nature of carcinoid tumors prior to entry into the accelerated growth phase, it is difficult to determine whether the response of SD observed in this group of patients is due to the cytostatic activity of thalidomide, or due to the natural history of the disease. Interestingly, this study demonstrated that 3 of 5 patients having PD in the 6 month period prior to initiation of thalidomide treatment demonstrated SD while on treatment. In order to better address this question, future studies could employ disease-free survival as an endpoint, identify the subset of patients who have already entered the accelerated tumor growth phase as subjects to assess response to treatment, employ biological endpoints, or investigate combination of thalidomide with other agents.

The toxicities observed in this trial are similar to those reported by others employing low dose (≤400 mg/day), single agent thalidomide. The most common side effects, as summarized in a recent review, include drowsiness, skin rash, constipation, peripheral neuropathy, xerostomia, orthostatic hypotension and dizziness, and neutropenia [16]. In fact, in the study of Drake et al. [5] of 20 men with androgen-independent prostate cancer, 100% of the patients

who had been on thalidomide for 6 months or longer developed subclinical peripheral neuropathy as measured by nerve conduction studies. Similarly, two patients in our study developed grade 3 peripheral neuropathy necessitating discontinuance of the drug, and five patients developed grade 3 dizziness that responded to dose reduction or drug holiday.

Chromogranins are a family of acidic, water-soluble glycoproteins that are stored within core vesicles in neuroendocrine cell granules [25]. Chromogranin-A (which is converted to pancreastatin by convertase-1) has been identified in carcinoid tumors isolated from the lung, stomach, small bowel, pancreas, gallbladder, colon, rectum, ovary, and liver [17], and has therefore been used as a tumor marker for carcinoid tumors. Two previous studies have reported serum pancreastatin elevation in 61% and 81%, respectively, of patients with carcinoid tumor [3,25]. In this study, elevated pancreastatin was observed in 100% of the patients, supporting its utility as a sensitive carcinoid tumor marker. However, it did not appear to be a good marker for tumor location or the presence or absence of carcinoid symptomatology. Furthermore, levels of pancreastatin correlated poorly with radiologic response. A wide range of other serum peptides proposed as possible tumor markers, including pancreatic polypeptide, substance P, gastrin, glucagon, neurotensin, VIP, GRP, and calcitonin, were also assessed in this study. Levels of these markers were infrequently elevated, and none could predict symptoms or correlation with radiologic response. Similarly, Goebel et al. [12] reported that neither serum Chromogranin-A nor gastrin levels correlated with gastrinoma tumor growth or extent of disease.

Previous work has shown that thalidomide inhibits the production of the pro-inflammatory cytokines IL-6 and TNF-α in peripheral blood mononuclear cells (PBMC) and selectively inhibits the expression of IL-6 and TNF-α mRNA [22]. This effect was felt to be due primarily to monocyte-derived TNF-α [23]. However, further work by this group demonstrated that thalidomide treatment suppressed intracellular levels of TNF-α in both CD3+ and CD3-PBMC and decreased the secretion of TNF-α from cells of the T cell line MOLT-4, suggesting that thalidomide is also capable of down-regulation of T-cell-derived TNF-α [23]. Oliver et al. [20] examined the plasma levels of TNF-α in patients with scleroderma being treated with thalidomide at an equivalent dose to that used in this study. Interestingly, thalidomide treatment induced an increase in plasma TNF-α levels at the 8-week timepoint. These results suggest that the immune response to thalidomide treatment is multifactorial and may differ among disease states and/or among patients. Similarly, in the small group of patients for whom we had total RNA available, we were not able to identify any consistent patterns in the gene expression of TNF-α, IL-1b, IL-6, or IFN-γ.

In summary, low dose single agent thalidomide was reasonably well tolerated among patients with metastatic carcinoid or islet cell tumor. Although the treatment was associated with disease stabilization in almost three-quarters of the patients, there were no objective complete or partial responses. Levels of serum pancreastatin and other peptide markers did not correlate with response to treatment. This trial does not support the routine use of low dose single agent thalidomide in patients with metastatic carcinoid or islet cell tumors.

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