First-line Cisplatin Plus Etoposide in High-grade Metastatic Neuroendocrine Tumors of Colon and Rectum (MCRC NET): Review of 8 Cases

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Abstract. *Background: The combination of cisplatin and etoposide is effective in the treatment of small cell lung carcinomas and other high-grade neuroendocrine tumors (NET). This combination has been considered as a default treatment for patients with high-grade NET of the colon and rectum (CRC). No formal series has yet described the activity of this regimen in this patient population. A retrospective study assessing the efficacy of cisplatin plus etoposide in metastatic CRC (MCRC) NET is reported. Patients and Methods: MCRC NET patients treated with cisplatin and etoposide were identified through the use of pharmacy and tumor registry records from a single institute for the period of 2003-2010. Responses of the identified patients were categorized using RECIST 1.1 (revised response evaluation criteria in solid tumors) guidelines. Results: Eight patients were identified with high-grade CRC NET who had been treated with cisplatin plus etoposide. One patient had a radiographic complete response and four had a partial response. The median progression-free survival was 4.5 months (2-9 months) and the median overall survival was 9.5 months (3.5-17 months). Conclusion: Patients with high-grade CRC NET have a high response rate to cisplatin and etoposide, which in most patients is short-lived, and the survival is limited to less than 1 year.*

Neuroendocrine tumors (NET) of the colon and rectum (CRC) are divided into three categories by the WHO classification: carcinoid tumors/well-differentiated NET with low-grade atypia and malignancy, malignant carcinoid/well-differentiated neuroendocrine carcinomas (NEC)-with intermediate features and poorly differentiated NET or small cell carcinoma with high-grade atypia and malignancy. Colorectal small cell carcinomas comprise 0.2-0.8% of all colorectal tumors (1, 2). The incidence of CRC NETs is rising in the United States, primarily as a result of increased incidental detection on screening. Symptoms of colorectal NETs include hematochezia, pain and change in bowel habits (3, 4).

Pathologically, high-grade CRC NETs are poorly differentiated carcinomas with distinctive cytoarchitectural features and are often immunoreactive for markers of neuroendocrine differentiation (5). The prognosis for high-grade CRC NET is poor, as most patients have metastatic disease at the time of diagnosis (6). In 2008, Landry *et al.* (7, 8) reported a 5-year survival rate of 17-20% and median survival of 20-31 months for CRC NET (stage IV) after study of 4,710 rectal NETs and 2,459 colon NETs. However, the SEER-based (Surveillance, Epidemiology and End Results database) data did not stratify outcome of stage IV CRC NET based on tumor grade or by treatment. The treatment of high-grade CRC NET remains largely non-standardized. Several studies have confirmed that combined chemotherapy with cisplatin and etoposide is the standard regimen in the treatment of small cell lung cancer. Because of the overlap in the genetic, pathological and clinical features of poorly differentiated extra-pulmonary NET with small cell lung cancer (9-11), the same regimen has been advocated for extra-pulmonary high-grade NET.

The aim of this report was to review the outcome of metastatic high-grade CRC (MCRC) NET tumors treated in a single-institute with cisplatin and etoposide.

Patients and Methods

A review of the Roswell Park Cancer Institute (RPCI) tumor registry and pharmacy records was performed for the period of 2003-2010. Only patients with a diagnosis of MCRC NET who were treated with cisplatin and etoposide at RPCI were eligible for analysis. All the staging radiographic studies were retrieved and re-evaluated. Objective responses, progression-free survival (PFS) and OS were determined based on RECIST 1.1 criteria.

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Key Words: Colorectal, neuroendocrine cancer, small cell cancer, chemotherapy, cisplatin, etoposide.

Table I. *Patient demographics and NET site.*

Patient	Age (years)	Gender	ECOG PS	Primary site	Metastatic sites	Pathology
1	55	M	1	Rectum	Liver	Poorly differentiated
2	83	F	1	Rectum	Liver, lung, lymph node	Poorly differentiated
3	51	F	2	Colon	Liver, peritoneum, lymph node	Poorly differentiated
4	71	M	0	Rectum	Liver, lymph node	Poorly differentiated
5	52	M	0	Colon	Liver	Poorly differentiated
6	78	F	1	Colon	Liver, lung, lymph node, bone	Poorly differentiated
7	31	M	0	Rectum	Liver, lymph node	Poorly differentiated
8	64	M	1	Rectum	Liver, lung	Poorly differentiated

ECOG PS: Eastern Cooperative Oncology Group performance score.

Statistical analysis was performed by use of the Kaplan-Meier method for estimating survival curves.

Results

Patient demographics. Eight patients with high-grade MCRC NET treated with first-line cisplatin and etoposide were identified. The median age was 64 years (31-83 years). All the patients had evidence of metastatic disease to the liver at presentation. One patient had concurrent lung metastases, two patients had concurrent distant lymph node involvement and one patient had concurrent lung, bone and distant lymph node involvement. Pathology was reported as poorly differentiated or high-grade in all eight patients. The patient demographics are detailed in Table I.

Treatment summary. All the patients received 21-day cycles of cisplatin plus etoposide. Cisplatin was administered at 80 mg/m^2 on day 1 and etoposide was administered at 80 mg/m^2/day on days 1-3. The median number of cycles administered was 5 per patient (range 2-12 cycles). Two patients received second-line therapy with cisplatin and irinotecan upon progression. (Table II)

Treatment efficacy. All eight patients were evaluable for radiographic response. One patient had a complete response (Figure 1a and b), four patients had a partial response and two patients had stable disease. One patient had progressive disease at 2 months. The median PFS was 4.5 months and median OS was 9.5 months (Table II, Figure 2a and 2b). The 12-week and 18-week PFS rates were 7/8 patients and 6/8 patients, respectively.

Table II. *Treatment and patient outcomes.*

Patient	Cycles (n)	PFS (months)	OS (months)	Best response	Second line CT
1	5	3	6	PR	
2	6	5	9.5	PR	
3	3	2	3.5	PD	Cisplatin-irinotecan
4	5	3.5+	3.5+	PR	
5	6	4.5	9.5	SD	
6	3	4.5	4.5	SD	
7	12	9	17	CR	Cisplatin-irinotecan
8	2	6+	6+	PR	

PFS: Progression-free survival; OS: overall survival; PR: partial response; PD: progressive disease; SD: stable disease; CR: complete response; CT: chemotherapy.

Discussion

MCRC NET treatment with cisplatin plus etoposide resulted in an objective response in five out of eight patients, a median PFS of 4.5 months and an OS of 9.5 months. The response was short-lived and most patients died within a year from diagnosis. The main limitation of this study was the small sample size.

Two prior studies on cisplatin and etoposide in advanced NET have been reported and the overall response rates were

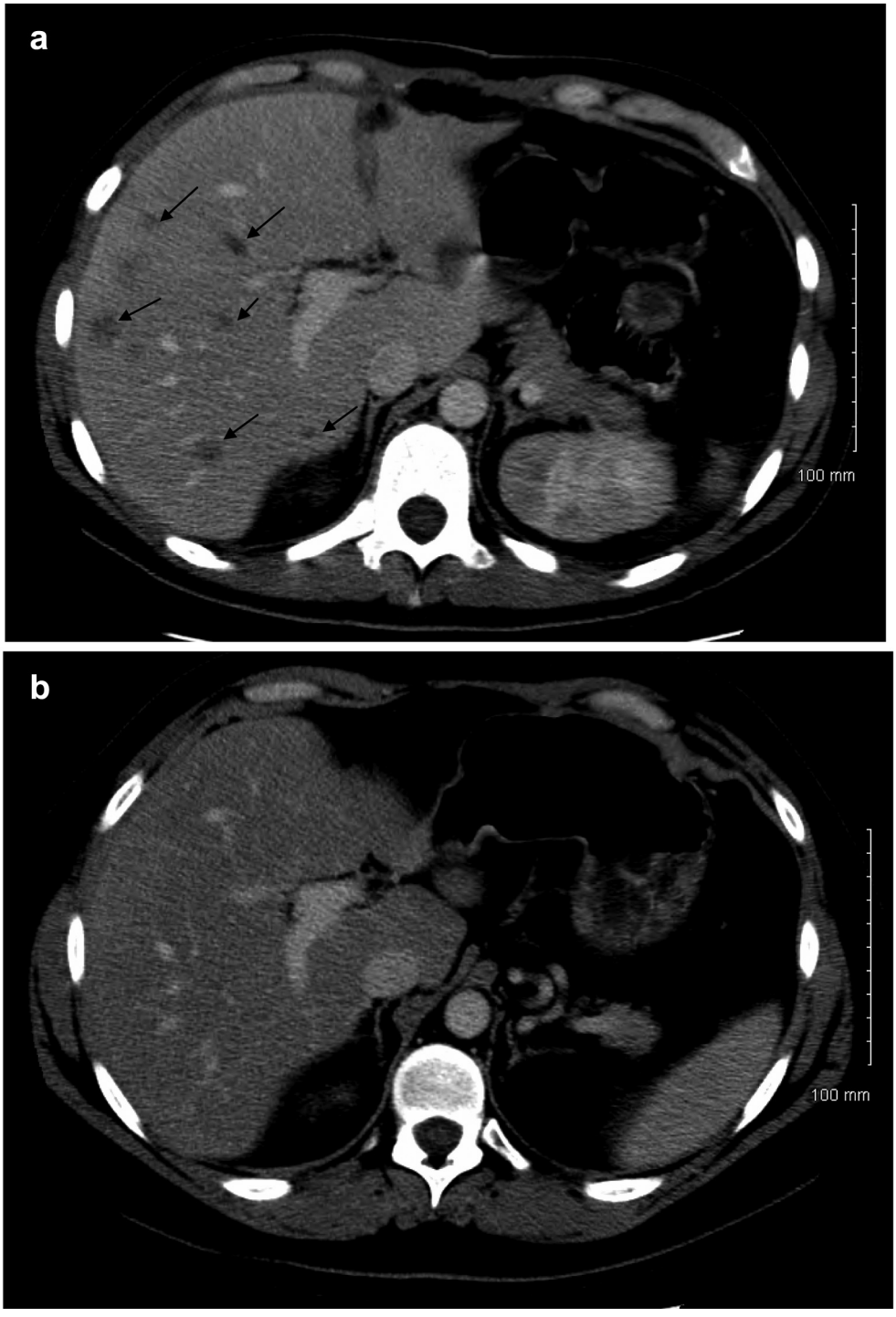

Figure 1. *a: CAT scan at a baseline of patient 7. b: CAT scan at complete response of patient 7.*

42 and 67% and the median survival was 15 and 19 months, respectively (12, 13). However, these two reports combined included only 5 patients with-high grade CRC NET. Bernick *et al*. studied 36 cases of colorectal/anal NETs (25 with stage IV), and the OS of this population was 10.5 months, confirming the poor prognosis of this group (5). Despite recommending cisplatin and etoposide, the outcome with this combination was not described in this series (5).

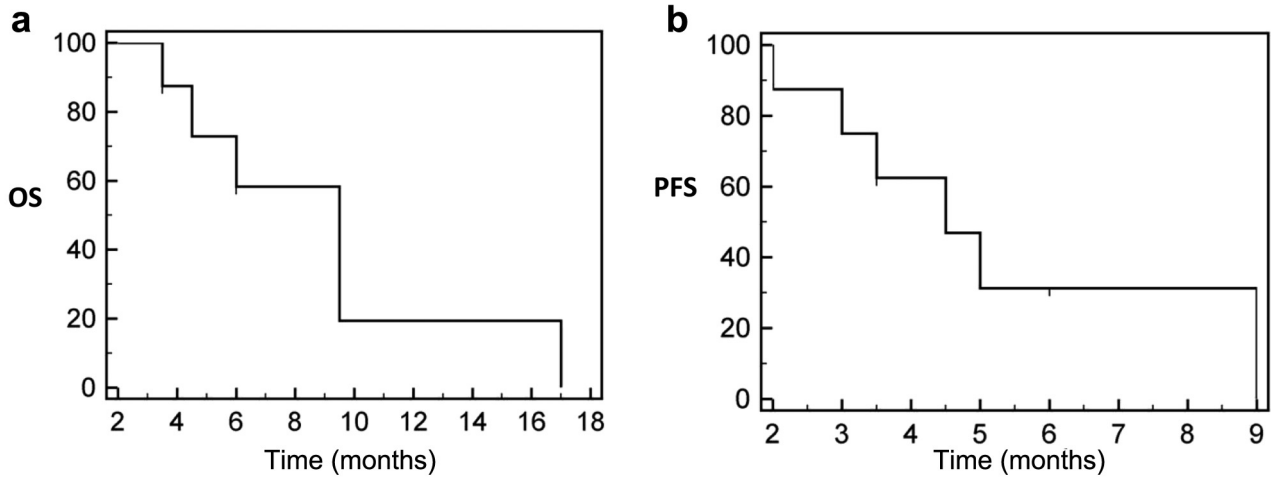

Figure 2. *a: Overall survival. b: Progression-free survival.*

Despite the small number of patients included in the present series, we believe that it represents the largest cohort of patients with high-grade MCRC NET treated with cisplatin and etoposide. The frequent objective responses associated with this combination support its use in this subgroup of patients.

References

1 Brenner B, Tang LH, Klimstra DS and Kelsen DP: Small-cell carcinomas of the gastrointestinal tract: a review. J Clin Oncol *22*: 2730-2739, 2004.

2 Kim JH, Lee SH, Park J, Kim HY, Lee SI, Nam EM, Park JO, Kim K, Jung CW and Im YH: Extrapulmonary small-cell carcinoma: a single-institution experience. Jpn J Clinl Oncol *34*: 250-254, 2004.

3 Kang H, O'Connel JB, Leonardi MJ, Maggard MA, McGory ML and Ko CY: Rare tumors of the colon and rectum: a national review. Int J Colorec Dis *22*: 183-189, 2007.

4 Staren ED, Gould VE and Warren WH *et al*: Neuroendocrine carcinomas of the colon and rectum: a clinicopathologic evaluation. Surgery *104*: 1080-1089, 1988.

5 Bernick PE, Klimstra DS, Shia J, Minsky B, Saltz L, Shi W, Thaler H, Guillem J, Paty P, Cohen AM and Wong WD: Neuroendocrine carcinomas of the colon and rectum. Dis Colon Rectum *42*: 163-169, 2004.

6 Shu-Juan Ni, Wei-Qi Cheng and Xiang Du: Pathologic research update of colorectal neuroendocrine tumors. World J Gastroenterol *16*: 1713-1719, 2010.

7 Landry CS, Brock G, Scoggins CR, McMasters KM and Martin RC II: A proposed staging system for rectal carcinoid tumors based on an analysis of 4701 patients. Surgery *144*: 460-466, 2008.

8 Landry CS, Brock G, Scoggins CR, McMasters KM and Martin RC II: "Proposed staging system for colon carcinoid tumors based on an analysis of 2,459 patients. J Am Coll Surg *207*: 874-881, 2008.

9 Anthony LB, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR, Wiseman GA, Benson AB III and Pommier RF: The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (NETs): well-differentiated NETs of the distal colon and rectum. Pancreas *39*: 767-774, 2010.

10 Clark OH, Benson AB, Berlin JD *et al*: Neuroendocrine tumors. National Comprehensive Cancer Network. *V2*: MS13, 2010.

11 Plockinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, De Herder WW *et al*: Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology *80*: 394-424, 2004.

12 Moertel CG, Kvols LK, O'Connell MJ and Rubin J: Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Cancer *68*: 227-232, 1991.

13 Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufie P and Aparicio T *et al*: Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer *81*: 1351-1355, 1999.

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