Oncology and Translational Medicine
DOI 10.1007/s10330-016-0166-6

December 2016, Vol. 2, No. 6, P279–P284

ORIGINAL ARTICLE

Clinical observation of rh-endostatin combined with chemotherapy as first line treatment for metastatic colorectal cancer*

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Abstract

Objective To analyze the efficacy and safety of Rh-endostatin combined with chemotherapy in the treatment of metastatic colorectal cancer.

Methods All 60 metastatic colorectal cancer patients were divided into the test group (n = 30) and the control group (n = 30). The control group was treated with chemotherapy regime FOLFOX4 (Oxaliplatin + Fluorouracil + Calcium Levofolinate), the test group was treated by Endostar combined with FOLFOX4 scheme.

Results The response rates were 53.3% in test group and 36.7% in control group respectively (P < 0.05), the disease control rate were 83.3% and 73.3% (P < 0.05). The median progression-free survival in test group and control group were 7.3 months versus 5.3 months (P < 0.05) and median overall survival were 11.6 months versus 9.3 months (P < 0.05). Among 27 cases of liver metastases were sub group analysis, difference on the test group and the control group response rate (RR) and disease control rate (DCR) had statistical significance (P < 0.05), but difference on progression free survival (PFS) and overall survival (OS) had no statistical significance (P > 0.05). The major toxicities were myelosuppression, gastrointestinal symptoms, neurotoxicity, most in grade I-II. After chemotherapy, quality of life (QOL) of patients were more improved than before treatment. After treatment the carcino embryonie antigen (CEA) and caner antigent 199 (CA199) levels decreased obviously, furthermore, the test group decreased more obviously than the control group.

Conclusion Rh-endostatin combined with chemotherapy in the treatment of metastatic colorectal cancer is safer and effective, and also improves PFS.

Key words: rh-endostatin; FOLFOX4 regimen; metastatic colorectal cancer

Received: 4 August 2016
Revised: 4 September 2016
Accepted: 25 September 2016

Currently, chemotherapy is the major treatment for metastatic colorectal cancer. With the emergence of new drugs, such as oxaliplatin and irinotecan, chemotherapy regimens can significantly prolong the survival time of patients; however, there are some clear limitations. Chemotherapy combined with targeted drugs, such as bevacizumab, improved the outcome in patients with metastatic colorectal cancer, but it is expensive. Fortunately, Chinese researchers have developed a targeted drug, recombinant human endostatin, which not only suppresses VEGF and angiogenesis to inhibit tumor metastasis, but is also less expensive [1–2]. Endostatin, a multi-targeted anti-angiogenesis drug, has been proven to be effective in the treatment of non-small cell lung cancer (NSCLC) [3–5], while its efficiency in colorectal cancer still needs further investigation. We initiated a prospective study in March 2008 to evaluate the efficacy and safety of endostatin in combination with FOLFOX4 in the treatment of metastatic colorectal cancer. Hepatic metastasis is crucial to patients' prognosis, and a major reason for death and organ failure in colorectal cancer patients. Thus, our study focused on patients with hepatic

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* Supported by a grant from the Nation Natural Sciences Foundation of China (No. 8127400).

metastasis.

Materials and methods

Clinical data

From March 2008 to March 2010, a total of 60 colorectal cancer patients with metastatic diseases from the Department of Oncology, Fuzhou General Hospital of Nanjing Military Command were enrolled in this study. The study cohort consisted of 38 men and 22 women. Patient ages ranged from 18 to 75 years (median 60 years). All patients had pathological adenocarcinomas and had received initial treatment or re-treatment. Inclusion criteria were: histologically confirmed stage IV adenocarcinoma of the colon or rectum; at least 1 measurable lesion; aged 18 years or older; no history of chemotherapy, or no chemotherapy for at least 1 month; Karnofsky scores ≥70; estimated survival time ≥3 months; no other primary cancers; normal routine blood test, and liver and kidney function test results; no limit to chemotherapy; and no other immune-related diseases, such as Crohn's disease, ulcerative colitis, rheumatism and rheumatoid diseases, and metabolic syndrome. All patients must have given their written informed consent. Exclusion criteria were: previous exposure to anti-angiogenesis therapy; any adverse reactions or unforeseen events; and patients lost to follow-up. The results from patients who experienced adverse events or who were lost to follow-up were not included in the final analysis. However, the drug efficacy in patients who received at least 2/3 of the treatment course was included in the final statistical analysis. Patients were randomly assigned to the test group or control group. Patients in these 2 groups were matched for clinico-pathological features, such as sex, age, ECOG scores, and location of the primary lesion (Table 1).

Treatment

Before the first course of chemotherapy, both the test and control groups underwent routine blood tests, liver and kidney functions tests, brain MRI, chest and abdomen CT, ECG, and bone scintigraphy. The control group received a FOLFOX4 chemotherapy regimen. Patients in the endostatin-FOLFOX group received 3–4 h of continuous infusion of endostatin from days 1–14. Cycles were repeated every 21 days. Patients in the test group received up to 4–6 cycles of FOLFOX4 plus endostatin. Patients received routine pretreatment before chemotherapy, and side effects were addressed with symptomatic treatment. Assessments of side effects were performed after the first cycle, while assessments of efficacy were performed after the second cycle. In patients for whom the treatment was effective, the therapy was continued for 4–6 cycles.

Table 1 clinicopathological features of 60 cases patients with advanced metastatic colorectal cancer (n = 30)

Clinicopathological features	rh-Endo + chemotherapy	Chemotherapy
Sex		
Male	20	18
Femal	10	12
The median age (years)	58 (23–79)	62 (27–75)
ECOG score		
0–1	20	21
2	10	9
Disease status		
Retreatment	16	14
Initial treatment	14	16
Primary tumor site		
Colon cancer	21	18
Colorectal cancer	9	12
The number of metastatic sites		
1	15	13
>1	15	17
Metastatic sites		
Lymph node	22	23
Liver	12	15
Others	6	8

Observation target and evaluation criterion

According to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0), patients were divided into stable disease (SD), progressive disease (PD), partial response (PR), and complete response (CR) groups. We used CR plus PR to calculate objective regression rates (RR), and CR plus PR and SD to calculate disease control rates (DCR). Tumor assessment was performed using CT; if the preliminary assessment showed PR or CR, the result was confirmed after 4 weeks. Adverse events were assessed according to NCI-CTC 3.0. Quality of life (QOL) was assessed using KPS scores. Progression free survival (PFS) refers to the period from randomized grouping to disease progression or death. Overall survival (OS) refers to the period from randomized grouping to death. The concentrations of carcino embryonie antigen (CEA) and cancer antigen 199 (CA199) before and after treatment were also assessed.

Follow-up

Follow-up was performed for all of the patients through a telephone call, at the outpatient clinic, or using medical records. The follow-up time was from the end of chemotherapy to the death of the patient, or until the patient was lost to follow-up. During the follow-up period, if disease progression occurred, the patient could choose their subsequent therapy, including second-line chemotherapy, traditional Chinese medicine, or the best

supportive therapy.

Statistical analysis

SPSS 17.0 was used to perform the statistical analysis. The chi-square test was used to analyze count data. The Kaplan-Meier method was used to plot the survival curve. A log-rank test was employed to compare the survival times between the groups. The variation of CEA and CA199 was analyzed using a paired t test. A two-sided *P* value of less than 0.05 was deemed statistically significant.

Results

Chemotherapy performance

The test group completed 153 cycles of chemotherapy, with an average of 5.1 cycles per patient. The control group completed 138 cycles of chemotherapy, with an average of 4.6 cycles per patient. There was no significant difference between the 2 groups ($P > 0.05$).

Efficacy

There were 60 patients for whom efficacy could be evaluated. In the test group, 2 patients achieved a CR, 14 patients achieved a PR, 9 patients achieved SD, and 5 patients achieved PD. The objective RR was 53.3% and the DCR was 83.3%. In the control group, 1 patient achieved a CR, 10 patients achieved a PR, 11 patients achieved SD, and 8 patients achieved PD. The RR was 36.7% and the DCR was 73.3%. Using a chi-square test, the RR and DCR in these 2 groups were significantly different ($P < 0.05$). The median follow-up time was 18.4 months. The median PFS in the test control groups was 7.3 months and 5.3 months, respectively, which was significantly different ($P < 0.05$; Fig. 1). The median OS in the test control groups was 11.6 months and 9.3 months, respectively, which was significantly different ($P < 0.05$; Fig. 2).

We further investigated efficacy in the 27 patients with liver metastasis. In the test group (12 cases), no patients achieved a CR, 6 patients achieved a PR, 4 patients achieved SD, and 2 patients achieved PD. The RR was 50% and the DCR was 83.3%. In the control group (15 cases), no patients achieved a CR, 5 patients achieved a PR, 5 patients achieved SD, and 5 patients achieved PD. The RR was 33.3% and the DCR was 66.7%. Using a chi-square test, statistical significance was found when the RR and DCR in these 2 groups were compared ($P < 0.05$). The median follow-up time was 18.4 months. The median PFS in the test and control groups was 4.3 months and 4.1 months, respectively, but there was no statistical difference ($P > 0.05$). The median OS in the test and control groups was 8.9 months and 8.8 months, respectively, and there was no statistical difference ($P > 0.05$).

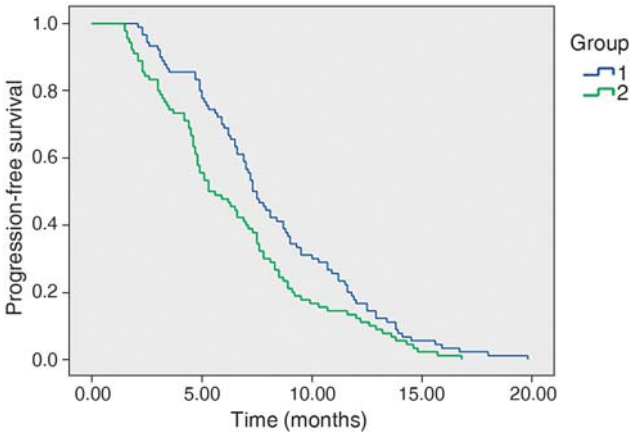

Fig. 1 Progression-free survival (PFS) curves of the experimental and control groups

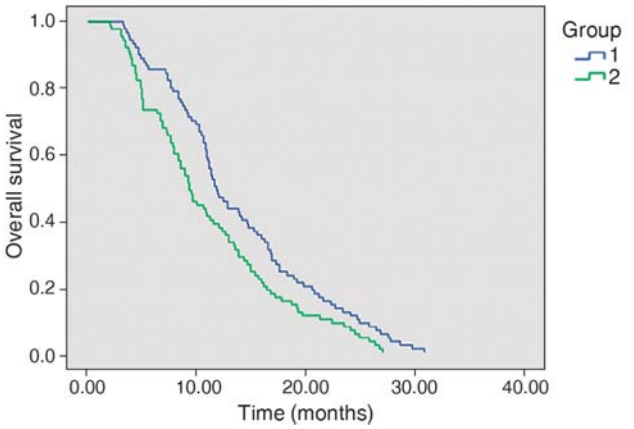

Fig. 2 Overall survival (OS) curves of the experimental and control groups

Adverse events

The major adverse events in these 2 groups were hematologic toxicity, gastrointestinal reactions, and neurotoxicity; these were mostly grade I–II and were relieved using supportive therapy. During the treatment, 1 patient developed arrhythmia, and 2 patients developed mild hypertension; both of these were considered to be endostatin-related and were relieved using supportive therapy. There were no statistical differences ($P > 0.05$; Table 2).

Quality of life evaluation

In the test group, 18 patients (60%) experienced improved QOL, 8 patients (26.7%) had a stable QOL, and 4 patients (13.3%) experienced a decline in their QOL. In the control group, 17 patients (56.7%) experienced improved QOL, 7 patients (23.3%) had stable QOL, and 6 patients (20%) experienced a decline in the QOL. There were no statistical differences ($P > 0.05$).

Table 2 Two treatment options cause toxicity of advanced colorectal cancer

Toxicity	Test groups (n = 30)				Control groups (n = 30)			
	I–II grade*		III–IV grade*		I–II grade		III–IV grade	
	n	%	n	%	n	%	n	%
Leukopenia	9	30	4	13.3	7	23.3	2	6.7
Thrombocytopenia	5	16.7	1	3.3	3	10	0	0
Anemia	8	26.7	1	3.3	8	26.7	0	0
Loss of appetite	9	30	3	10	7	23.3	3	10
Fatigue	12	40	2	6.7	10	33.3	1	3.3
Nausea and vomiting	6	20	1	3.3	3	10	0	0
Diarrhea	8	26.7	2	6.7	7	23.3	1	3.3
Oral mucositis	2	6.7	0	0	2	6.7	1	3.3
Peripheral neurotoxicity	11	36.7	0	0	12	40	0	0
Cardiac events	1	6.7	0	0	0	0	0	0
Hypertension	2	6.7	0	0	0	0	0	0
Hemorrhage	0	0	0	0	0	0	0	0
Abnormal liver function	5	16.7	0	0	6	20	0	0
Renal dysfunction	13	3.3	0	0	2	6.7	0	0

Compared with the control groups, * $P < 0.05$

Table 3 changes of CEA and CA199 before and after experimental groups treatment

Tumor markers	Test groups (n = 30)		Control groups (n = 30)	
	Before treatment	After treatment	Before treatment	After treatment
CEA (ng/mL)	428.32 ± 337.54	11.81 ± 3.23*#	432.51 ± 321.36	54.81 ± 12.01*
CA199 (μg/mL)	2667.71 ± 1209.11	102.25 ± 23.17*#	2059.88 ± 1526.45	363.89 ± 245.62*

Compared with before treatment, * $P < 0.05$; After treatment, compared with control groups, # $P > 0.05$

Tumor biomarkers

After treatment, the serum levels of CEA and CA199 were down-regulated in both groups, compared with the serum levels before treatment. Statistical significance was found in both groups ($P < 0.05$). As compared with the control group, the serum levels of CEA and CA199 in the test group showed a larger down-regulation, which was significantly different between the 2 groups ($P < 0.05$; Table 3).

Discussion

As the first anti-angiogenesis drug on the market, recombinant human endostatin can inhibit the migration of endothelial cells, suppress tumor angiogenesis, and block the nutrition supply to tumor cells to inhibit tumor progression and invasion [6]. A phase III randomized controlled clinical trial of an endostatin and NP regimen for NSCLC demonstrated that endostatin combined with an NP regimen can markedly improve the RR and median TTP of advanced NSCLC, and has a good level of safety [3].

Colorectal cancer is one of the most common digestive system carcinomas. Many patients present with metastatic disease and their median OS is less than 2 years. Standard first-line treatment includes fluorouracil with oxaliplatin or irinotecan. The most commonly used regimens are FOLFOX, FOLFIRI, or XELOX. Hurwitz *et al* [7] performed a phase III clinical trial and found that an irinotecan-based regimen combined with bevacizumab can prolong PFS and OS. This was the first time it has been proven that anti-angiogenesis therapy can have substantial survival benefits for colorectal cancer patients. Likewise, an oxaliplatin-based regimen combined with bevacizumab showed better short-term and long-term effects than a chemotherapy regimen alone [8]. As these effects may be attributable to the anti-VEGF role of bevacizumab, it offers a treatment option for metastatic colorectal cancer patients [9–11]. Thus, we hypothesized that other anti-angiogenesis drugs may improve the efficacy of a chemotherapy regimen in colorectal cancer patients. Basic studies on the inhibition of lymphatic endothelial cells in colorectal cancer have achieved good results, as have studies investigating anti-angiogenic agents [12–13].

Hut *et al* [14] reported the results of endostatin combined with chemotherapy for metastatic colorectal cancer. Thirty-one patients were enrolled in their study and received endostatin combined with oxaliplatin, irinotecan, or capecitabine-based chemotherapy. Among all of the patients, 12 achieved a PR, 11 achieved SD, and 8 patients achieved PD. The clinical effective rate was 38.7% (12/31) and the clinical benefit rate (CBR) was 74.2% (23/31). Among the 13 patients who were receiving their first treatment, 9 achieved a PR and the clinical benefit

rate was 100%. For patients who were receiving their second or third line treatment, the clinical effective rate was 16.7%. Zhuang *et al* [15] reported retrospective data on the comparison of capecitabine combined with irinotecan or capecitabine combined with endostatin for oxaliplatin failure in 45 metastatic colorectal cancer patients. In the irinotecan group, the RR was 32.0%, the CBR was 72.0%, and the TTP was 6.2 months. In the endostatin group, the RR was 55.0%, the CBR was 90.0%, and the TTP was 10.6 months. The differences between the 2 groups were significant ($P < 0.05$). The OS in these 2 groups was 15.2 months and 16.01 months, respectively. Taken together, endostatin combined with chemotherapy can be effective for metastatic colorectal cancer patients.

Our study enrolled colorectal cancer patients with stage IV disease and multiple metastases; the QOL scores in this group were low. The study design was prospective, and the test group was treated with endostatin combined with FOLFOX4, while the control group was treated with FOLFOX4 alone. The results showed that in the test group and control group, the RR was 53.3% and 36.7%, the DCR was 83.3% and 73.3%, the PFS was 7.3 months and 5.3 months, and the OS was 11.6 months and 9.3 months, respectively. Differences between the 2 groups were statistically significant ($P < 0.05$). Thus, the test group showed a significant improvement in the RR, DCR, and OS. This study indicated that endostatin combined with chemotherapy is superior to chemotherapy alone.

The morbidity and mortality of colorectal cancer have been increasing year by year, and about 50%–60% of colorectal cancer patients have liver metastases. Twenty to forty percent of patients have liver metastases at the time of diagnosis [16–17]. Some researchers have demonstrated that liver metastasis is the main reason for hepatic failure and death. In order to test whether patients with liver metastases could benefit from Endostar combined with chemotherapy, 27 cases of liver metastases were further analyzed. Our study indicated that there was a significant difference ($P < 0.05$) in RR and DCR between the test group and the control group, but not in PFS and OS. This result suggested that RR and DCR were greatly improved in the test group, whereas the OS was not prolonged. Meanwhile, this also proved that liver metastases were important factors that affected the prognosis; complete liver metastases resection is the only curative option for patients with colorectal cancer liver metastases. A number of studies show that the 5-year event-free survival of colorectal cancer liver metastases patients who do not undergo surgery is about 0.5% [18]. By contrast, the 5-year event-free survival of those who are suitable for surgery initially or after conversion therapy is 30%–50%. However, only 15%–20% of patients are suitable for radical resection, and most cannot undergo surgery for various reasons. Conversion therapy can transform 10%–30% of unresectable liver metastases into resectable disease, which has significantly increased the resection rate, prolonged survival, and improved the prognosis. Based on the literature and our research, colorectal cancer liver metastases remain challenging. To date, to prolong survival and improve QOL, the most effective approach is still comprehensive treatment, including surgery, chemotherapy, radiotherapy, interventional therapy, and targeted therapy [19].

No additional adverse events were observed in the endostatin group, showing that all of the patients can tolerate the administered therapy. After treatment, the QOL of patients from both groups was markedly improved, and the patients were able to receive further therapy. As well-known clinical biomarkers for colorectal cancer, CEA and CA199 cannot act as specific diagnostic criteria; however, they can be meaningful for follow-up of patients who have undergone surgery or completed chemotherapy. The down-regulation of CEA and CA199 may indicate remission or control of the tumor [20]. Based on the results of the current study, the serum levels of CEA and CA199 were down-regulated after treatment. Furthermore, compared with the control group, the serum levels of these biomarkers were more significantly down-regulated in the test group, which further demonstrated that endostatin combined with chemotherapy is superior to chemotherapy alone.

In conclusion, this trial provides confirmation that endostatin can enhance the anti-tumor effect of FOLFOX4 when used as the first-line treatment for metastatic colorectal cancer. Endostatin can prolong the survival time of patients without increasing the risk of adverse events. In addition, this trial found that endostatin plus FOLFOX4 cannot prolong the survival time of colorectal cancer patients with liver metastasis, which is a limitation of this regimen. Due to the small sample of this trial, the results may be somewhat biased. Thus, a clinical trial with a large sample population is needed to demonstrate the survival benefit of endostatin plus chemotherapy for metastatic colorectal cancer.

References

1. Zhou ZW, Wan DS, Wang GQ, *et al*. Inhibitory effect of angiogenesis inhibitor YH-16 in combination with 5-FU on liver metastasis of colorectal cancer. Cancer (Chinese), 2006, 25: 818.
2. Qin SK, Liu XF, Wang L, *et al*. Clinical studies of recombinant human endostatin combined with chemotherapy in the treatment of pulmonary outer advanced cancer. Chin Clin Oncol (Chinese), 2007,12: 728.
3. Wang JW, Sun Y, Liu YY. Recombinant human endostatin combined with NP therapy advanced NSCLC randomized,double-blind,controlled, multi—center clinical study period III. Chin J Lung Cancer, 2005, 8: 283–290.
4. Xia KY. Simmered published endostar phase IV clinical study latest

developments. Chin Healthcare Innovation (Chinese), 2010, 5: 96.
5. Tian Y, Tian Z, Wu K, *et al*. The efficacy and safety meta-analysis of endostar combined with platinum-based chemotherapy treatmenting patients with advanced no-small cell lung cancer. J Chongqing Med University (Chinese), 2012, 37: 151–157.
6. Gao S, Yang XH, Fan YB, *et al*. Effects and preliminary study on the mechanism of endostar on proliferation and apoptosis of the HUVECs induced by tumor supernatant fluid. Mod Oncol (Chinese), 2011, 19: 2184–2187.
7. Hurwitz H, Fehrenbacher L, Novotny W, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med, 2004, 350: 2335–2342.
8. Mikami Y, Tamura N, Akiyama M, *et al*. A case of pathologically complete response in a patient with locally advanced sigmoid colon cancer after chemotherapy including bevacizumab/FOLFOX4. Gan To Kagaku Ryoho, 2014, 41: 777–779.
9. Petrelli F, Coinu A, Cabiddu M, *et al*. Prognostic factors for survival with bevacizumab-based therapy in colorectal cancer patients: a systematic review and pooled analysis of 11,585 patients. Med Oncol, 2015, 32: 456.
10. Soga Y, Ito D, Asano H, *et al*. Continuation of chemotherapy with bevacizumab for advanced and recurrent colorectal cancer. Gan To Kagaku Ryoho, 2013, 40: 1341–1345.
11. Chai YL, Xiao JX, Suo AL, *et al*. A clinical research of bevacizumab combined with chemotherapy in the treatment of advanced eolorectal cancer. Mod Oncol (Chinese), 2013, 21: 2040–2043.
12. Sohn BS, Park SJ. Single-nucleotide polymorphisms in the vascular endothelial growth factor pathway and outcomes of patients treated with first-line cytotoxic chemotherapy combined with bevacizumab for advanced colorectal cancer. Oncology, 2014, 87: 280–292.
13. Li XQ, Ji FX, Lin MZ, *et al*. Clinical observation of Endostar combined with chemotherapy in treatment of advanced gastrointestinal cancer. Mod Oncol (Chinese), 2012, 20: 570–572.
14. Hu GY, Zhang L, Mei Q, *et al*. Term eficacy of recombinant human endostatin combined with chemotherapy therapying advanced metastatic colorectal cancer. Acta Med Univ Seientiae Technol Huazhong (Chinese), 2009, 38: 391–393.
15. Zhuang CP, Cai GY, Li Y, *et al*. Capecitabine combined with endostatin or irinotecan treatment advanced metastatic colorectal cancer with oxaliplatin resistance. Chin J Cancer Biother (Chinese), 2009, 16: 175–180.
16. Liu DJ. Simultaneous liver metastases of coloreetal cancer operationtime. Chin J Dig Surg (Chinese), 2012, 7: 143–145.
17. Beppu T, Emi Y, Tokunaga S, *et al*. Liver resectability of advanced liver-limited colorectal liver metastases following mFOLFOX6 with bevacizumab (KSCC0802 Study). Anticancer Res, 2014, 34: 6655–6662.
18. Jones RP, Jackson R, Dunne DF, *et al*. Systematic review and meta-analysis of follow-up after hepatectomy for colorectal liver metastases. Br J Surg, 2012, 99: 477–486.
19. Cai GX, Cai SJ. Multi-modality treatment of colorectal liver metastases. World J Gastroenterol, 2012, 18: 16–24.
20. Li Y. Clinical value of gastric cancer and colorectal cancer serum tumor markers. Gastroenterology (Chinese), 2008, 13: 705–706.

DOI 10.1007/s10330-016-0166-6
Cite this article as: Wang WW, Huang SS, Huang XY, *et al*. Clinical observation of Rh-endostatin combined with chemotherapy in the first line treatment of metastatic colorectal cancer. Oncol Transl Med, 2016, 2: 279–284.