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What is This?

Anticancer Effects of HESA-A in Patients With Metastatic Colon Cancer

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Background: HESA-A is a natural biological compound of herbal–marine origin. The aim of this study was to investigate the therapeutic effects of HESA-A in patients with metastatic colon cancer. *Methods:* Fifty consecutive patients with end-stage colon cancer and liver metastasis at the Cancer Research Center of Tehran University of Medical Sciences were studied. Patients received HESA-A 50 mg/kg/d orally in 2 to 3 divided doses for 6 months. The patients were assessed at the start and end of the 1st, 2nd, 4th, 8th, 12th, 16th, 20th, and 26th weeks of the study. The Karnofsky Performance Scale questionnaire was completed for each patient. *Results:* The mean Karnofsky performance score increased from 33.6 ± 9.8 to 63.3 ± 11 after 10 weeks of study. No significant hepatic or hematological adverse effects were seen during the study. *Conclusion:* It seems that HESA-A is an effective and safe anticancer drug, which can be used in selected patients.

Keywords: HESA-A; cancer; antioxidant; colorectal; side effects

Introduction

Colorectal cancer is the most common malignancy of the gastrointestinal tract and the second most common cause of cancer-related death in the world.[1] It is the second most common cancer in Europe after breast cancer and the second most common cause of cancer death following lung cancer.[2] Although the prognosis in the majority of patients with early phase diagnosis is good, in patients with diagnoses in the advanced phase prognosis is poor. The incidence of colorectal cancer in Iran has been reported to be 8.2 and 7.0 per 100 000 for men and women, respectively.[3]

However, treatment is a challenging issue in patients with metastatic and advanced disease. The toxicity of chemical anticancer agents against healthy cells and body organs is a major limitation of application of these drugs.[4,5] The use of antioxidants has been shown to provide some protection against cancers.[6,7] Selenium, zinc, nickel, and titanium are among the elements with antioxidant properties that have been studied.[8-13]

HESA-A (a natural biological compound) is a herbal–marine mixture, including *Penaeus* (*Melicertus*) *latisulcatus* (king prawn; family Penaeidae), *Carum carvi* L. (Apiaceae), and *Apium graveolens* L. (Apiaceae), with anticancer properties.[14,15] Although the exact mechanism of action of HESA-A on tumor cells is not fully understood, it appears to have multiple pharmacological effects.[15] HESA-A includes mineral constituents (50%), organic constituents (45%), and water (5%). The mineral constituents are a mixture of calcium carbonate, magnesium sulfate, potassium sulfate, sodium sulfate, magnesium phosphate, potassium phosphate, and sodium phosphate. Low percentages of other elements such as Br, Sr, Ti, Mn, Ni, As, Ag, Cu, Zn, W, Tm, Lu TI, Er, Va, Cs, Ba, and Te are found in salt or complex forms in the HESA-A compound.[15,16] Some studies have demonstrated the antitumor properties of some of these elements.[11-13,17-19] The anticancer effects of HESA-A has been the subject of both in vivo and in vitro studies.[20,21]

The aim of the present study was to investigate the therapeutic effects of HESA-A in patients with metastatic colon cancer.

Materials and Methods

In a prospective noncontrolled clinical trial, 50 patients with advanced colon cancer and liver metastasis (end stage) at the Cancer Research Center of Tehran University of Medical Sciences were studied. The inclusion criteria were colon cancer with metastasis to liver (more than 50% involvement of liver) documented by spiral CT scan, pathology report, and patient history and

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having no therapeutic plans in the last 2 months based on existing scientific references and an expected survival of less than 1 month (as judged by clinical findings). Patients with cardiovascular, cerebrovascular, respiratory, or hematological diseases and an ongoing infectious process were excluded from the study. Written informed consent was obtained from the patients before enrollment. The study protocol was approved by the Research Ethics Committee of Cancer Research Center of Tehran University of Medical Sciences. The study was conducted according to the Helsinki Declaration.

In this study, HESA-A was prepared as a biologically active compound of herbal and marine origin, in 500 mg sterile capsules.[16,22] The active component of the drug was passed through 0.22 μm filters and sterilized before being encased in gelatin capsules as neutral powder (pH = 7.4).[16] The drug was administered orally at a dose of 50 mg/kg/d in 2 to 3 divided doses for a period of 6 months. During the study, the patients received morphine at 20 to 100 mg doses. The patients were assessed at the start and end of the 1st, 2nd, 4th, 8th, 12th, 16th, 20th, and 26th weeks of the study, and hematological and hepatic biochemical indices were measured.

Additionally a questionnaire including the Karnofsky Performance Scale was completed for each patient. The Karnofsky Performance Scale index allows patients to be classified in terms of their functional impairment. This can be used to compare the effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses. Hematological indices were measured with a H-1 Coulter machine, and hepatic indices were measured using a RA-1000 Technicon autoanalyzer. All blood samples were taken in the morning and in a fasting state.

Study data were analyzed using SPSS software version 11.5 for Windows. The ANOVA test was used for repeated measures, the paired t test was applied for comparison of quantitative variables, and the χ^2 test was used for comparison of ratios and percentages.

Results

In this clinical trial, 50 patients (26 men and 24 women) with metastatic colorectal cancer were recruited. The mean age of the patients was 63.3 ± 11 years (40-70 years). The patients were monitored for drug side effects and changes in their hematological indices. Only 8 patients (16%) displayed drug side effects, which ranged from mild, including anorexia (in 4 patients, 8%), to moderate, including weakness (1 patient), headache (1 patient), and nausea and vomiting (2 patients; total in 4 patients, 8%). Based on the physician's clinical judgment, only in 4 cases (8%) could the symptoms be related to the drug.

Table 1. Patient Performance Assessed by Karnofsky Criteria

Patient Status	Before the Study	After the Study	P Value
Capable of work and normal activity, n (%)	0 (0)	17 (34)	<.001
Unable to work, able to live at home, n (%)	32 (64)	7 (14)	<.001
Unable to care for self, n (%)	43 (86)	1 (2)	<.001
Mean Karnofsky performance score (mean ± SD)	33.6 ± 9.8	63.3 ± 11	<.001

NOTE: SD = standard deviation.

The mean daily dose of morphine administered to the patients decreased from 50 ± 15 mg before the study to 35 ± 10 mg after the study ($P < .05$). Mean fasting blood glucose level of patients did not change during the study period ($P > .05$). Assessment of patients with the Karnofsky Performance Scale showed a significant improvement in their performance after the 10th week of the study (Table 1). Mean Karnofsky Performance scores of the patients rose from 33.6 ± 9.8 at the beginning of the study to 63.3 ± 11 at the end of the 10th week of the study ($P < .001$; Table 1).

Based on the assessment of liver enzymes, the hepatic function of patients improved significantly during the study (Table 2). As shown by the paired t test, there was a significant decrease in the level of hepatic enzymes during the study (Table 2). No significant changes were observed in hematological parameters during the study period (Table 3).

In all, 88% and 84% of the patients remained in the study for more than 18 weeks and 24 weeks, respectively (Figure 1). Only 37 patients survived until the end of the study (26 weeks).

Discussion

This study demonstrated the anticancer effects of HESA-A, a herbal–marine compound, in patients with end-stage metastatic colon cancer. After 6 months of therapy, patients' levels of functional impairment (according the Karnofsky performance scale) improved significantly. Also, no significant adverse effect was seen during the study.

The lack of selectivity for tumor cells that is associated with conventional cancer chemotherapy is the main cause of chemotherapy complications and failure of anticancer agents. Many complementary and alternative medicine studies are focused on products obtained from plants, animals, or other natural sources. HESA-A inhibits the growth of cancer cells selectively and in a

Table 2. Changes in the Hepatic Parameters of Patients With Colorectal Cancer
and Liver Metastasis Under Treatment With HESA-A[a]

Week	Bilirubin (Direct) SD ± Mean	Bilirubin (Total) SD ± Mean	Alkaline Phosphatase SD ± Mean	SGPT SD ± Mean	SGOT SD ± Mean
Week 0 (n = 50)	112 ± 27	96 ± 32.5	582 ± 310	12 ± 6.1	5.2 ± 2.4
Week 2 (n = 50)	98 ± 26.2	90 ± 26.1	551.2 ± 282	10.5 ± 5.4	4.6 ± 2.1
Week 4 (n = 50)	81 ± 21.1	78 ± 21.4	502 ± 261	8.2 ± 4	3.1 ± 2.2
Week 6 (n = 50)	76 ± 22.3	62 ± 18.2	481 ± 226	7.1 ± 3.6	3.6 ± 1.9
Week 12 (n = 46)	64 ± 20.1	51 ± 17.1	407 ± 218	6.2 ± 3.2	3.1 ± 1.8
Week 20 (n = 39)	53 ± 21.6	40 ± 18.2	391 ± 180	5.3 ± 3.1	3.2 ± 1.6
Week 26 (n = 37)	51 ± 19.8	38 ± 16.4	396 ± 169	5.6 ± 2.9	2.9 ± 1.7
P value	<.0001	<.0001	<.0001	<.0001	<.0001

NOTE: SD = standard deviation; SGPT = serum glutamic pyruvate transaminase; SGOT = serum glutamic oxaloacetic transaminase.
[a]ANOVA test was used for analysis.

Table 3. Changes in the Hematological Parameters of Patients With Liver Cancer Under Treatment With HESA-A[a]

Week	RBC SD ± Mean	Hb mg/dL SD ± Mean	WBC SD ± Mean	LYM (%) SD ± Mean	PMN (%) SD ± Mean	EOS (%) SD ± Mean
Week 0 (n = 50)	4.6 ± 0.7	12.1 ± 2.4	8321 ± 2341	34.1 ± 10	69.2 ± 9.2	2.2 ± 1.8
Week 2 (n = 50)	4.5 ± 0.6	11.8 ± 2.2	8165 ± 2156	33 ± 10.2	61.5 ± 11.8	2.1 ± 1.2
Week 4 (n = 50)	4.6 ± 0.6	12.4 ± 2.6	7809 ± 2658	32.2 ± 8.9	60.3 ± 16.3	1.8 ± 0.77
Week 6 (n = 50)	4.4 ± 0.6	11 ± 2.7	7940 ± 3672	31.6 ± 9.3	56.1 ± 8.6	1.4 ± 0.6
Week 12 (n = 42)	4.2 ± 0.8	11.6 ± 2.6	7535 ± 2836	33.4 ± 9.1	59.7 ± 8.4	1.6 ± 0.6
Week 26 (n = 37)	4.5 ± 0.9	12.2 ± 2.5	7983 ± 2889	32.6 ± 7.8	64.1 ± 6.8	1.7 ± 0.8
P value	>.05	>.05	>.05	>.05	>.05	>.05

NOTE: SD = standard deviation; RBC = red blood cells; Hb = hemoglobin; WBC = white blood cells; LYM = lymphocytes; PMN = polymorphonuclear leukocytes; EOS = eosinophils.
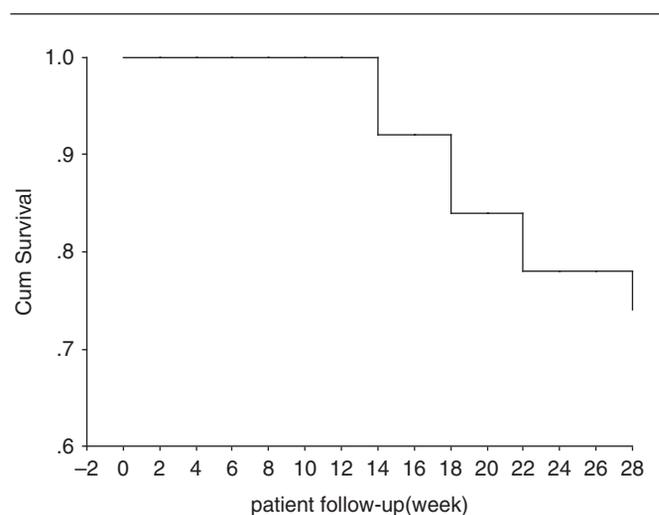[a]ANOVA test was used for analysis.

Figure 1. Cumulative survival of patients under treatment with HESA-A during the 26 weeks of the study.

dose-dependent manner. At the highest concentration (5.4 mg/mL), HESA-A completely inhibits the growth of cells, and this effect gradually decreases as the dose is reduced. HESA-A is not cytotoxic toward normal cell lines but only toward cancer cells. A major concern in this selectivity effect is the possible interaction with the cell DNA. Apoptotic effects of HESA-A may also have a major role in its anticancer properties.[16,23]

HESA-A is rich in trace elements. Se, Zn, Ni, and Ti are among the elements with antioxidant properties that have been studied.[24] The presence of these elements and antioxidant compounds in HESA-A may have a role in its antitumor properties. Titanium has displayed remarkable anticancer effects in drug complexes. Other studies have demonstrated the anticancer effect of selenium in stopping neoplastic growth in rats.[17] Vanadium-containing compounds have exhibited anticancer properties, and nickel has been shown to have antimitotic properties in laboratory studies on rats.[18,19] Therefore, the effects of HESA-A against cancer cells are possibly a result of the presence of these trace elements in its composition. In toxicological studies, HESA-A did not induce any biochemical, hematological, or histopathological signs of toxicity.[15,20]

The small sample size, absence of a control group, and no assessment of patients' quality of life are limitations of this study.

It appears that HESA-A is an effective and safe anticancer drug with selective effect, which may be used in selected patients. However, further prospective controlled

clinical trials with large sample sizes are warranted to properly understand the mechanisms of action of HESA-A and evaluate its long-term effects on the survival and quality of life of patients with cancer and even its probable side effects.

Acknowledgments

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