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Therapeutic Effects of HESA-A in Patients With End-Stage Metastatic Cancers

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Abstract

Background: After cardiovascular disease, cancer is the most common cause of death. HESA-A is a natural product of herbal and marine origin. The aim of this study was to investigate the beneficial effects of HESA-A in patients with end-stage metastatic cancers. *Methods:* In this clinical trial, 30 consecutive patients (18 men, 12 women) with end-stage cancers 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 3 months. At the start and end of the 1st, 4th, 8th, and 12th weeks of the study, the patients were assessed and hematological and hepatic biochemical indices were measured. Also, the Karnofsky Performance Scale questionnaire was completed for each patient. *Results:* The mean age of patients was 56.23 ± 12.10 years. Mean Karnofsky Performance Scale scores of the patients increased from 48 ± 14.36 to 78.42 ± 15.37 after 12 weeks of treatment. A total of 90.4% of the patients who remained in the study were alive for 12 weeks. No significant hepatic or hematologic adverse effect was seen during the study. *Conclusion:* HESA-A appears to be an effective and safe anticancer compound that may increase survival of end-stage patients and can be used in selected cases. Further prospective controlled clinical trials with large sample size and longer follow-up period are warranted to 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 as well as its unfavorable side effects.

Keywords

HESA-A, cancer, antioxidant, side effects

Introduction

After cardiovascular diseases, cancer is the second major cause of death in developed countries, accounting for 24% of all deaths.[1] Distant metastasis, including liver metastasis is the leading cause of death in most neoplasms. Once cancer is diagnosed, a variety of possible therapeutic options are considered. The choice of therapy is dependent on the type, stage and grade of cancer (the extent of its progress). The most frequently offered options in the treatment of cancer include surgery, radiotherapy, and chemotherapy. Each may be used alone or in combination with others. Systemic chemotherapy is the final line of treatment for metastatic cancers.

However, treatment is a challenging issue in the patients with metastasis. The toxic effects of chemical anticancer drugs on healthy cells and body organs is the main limitation on application of these drugs.[2,3] Considering adverse effects of chemical anticancer agents on normal body tissues, the need to find new drugs with selective effects on cancer tissue is well recognized.

Antioxidant agents have been shown to provide some protective effects against cancers.[4,5] Selenium, zinc, nickel, and titanium are among the elements with antioxidant properties that have been studied.[6-11]

HESA-A is a biologic drug with herbal–marine origin, a natural biological compound, (patented by Iranian researchers) composed of plant and marine materials, including *Penaeus latisculatus* (king prawn), *Carum carvi*, and *Apium graveolens* with anticancer properties,[12,13] which is prepared by a special process (proprietary to the patent holder). It has selective toxicity against cancer cells. Although the exact mechanism of action of HESA-A on tumor cells is not

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fully understood, it appears to have multiple pharmacological effects.[13]

HESA-A includes mineral constituents (50%), organic constituents (45%), and water (5%). It contains inorganic elements, including CaO (43.787%), P_2O_5 (6.63%), Na_2O (3.689%), MgO (2.897%), SO_3 (2.193%), K_2O (1.988%), SiO_2 (1.09%), Fe_2O_3 (0.375%), Al_2O_3 (0.354%), and low percentage of other elements such as Br, Sr, Ti, Mn, Ni, As, Ag, Cu, Zn, W, Tm, Lu Tl, Er, Va, Cs, Ba, and Te that have been detected in salt or complex forms in HESA-A compound.[13,14] Studies have demonstrated the antitumor properties of some of these elements.[9-11,15-17] The anticancer effects of HESA-A have been investigated in both in vivo and in vitro studies.[18,19]

The aim of the present study was to investigate anticancer effects of HESA-A in patients with end-stage cancer and liver metastasis.

Materials and Methods

In a prospective noncontrolled clinical trial, 30 patients with advanced cancers and liver metastasis (end stage) at the Cancer Research Center of Tehran University of Medical Sciences were studied. The mean age of patients was 56.23 ± 12.10 years (range 29 to 75 years). The inclusion criteria were advanced cancer with liver metastasis (more than 50% involvement of liver) documented by spiral computed tomography (CT) scan, pathology report, and patient history, having no therapeutic plans in the past 2 months based on existing scientific references and an expected survival of less than 1 month (as judged by clinical findings). The patients had received different available therapeutic options before the study (at least 2 months ago).

Patients with cardiovascular, cerebrovascular, respiratory, or hematological diseases or a current 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 the 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.[14,20] 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).[14]

The drug was administered orally at a dose of 50 mg/kg/d in 2 to 3 divided doses for a period of 3 months. During the study, the patients received morphine at 20 to 100 mg doses. At the beginning of study before drug administration, and at end of the 1st, 4th, 8th, and 12th weeks of the study, patients were assessed for body weight, appetite, abdominal pain, and vital signs and hematological and hepatic biochemical indices were measured. Body weight was measured using a standard balance. Abdominal pain and appetite were determined and monitored using a questionnaire with 4 grades by direct interview with the patient. A score of zero was assigned for negative abdominal pain and full appetite.

Additionally, a questionnaire, including the Karnofsky Performance Scale was completed for each patient. The Karnofsky Performance Scale Index classifies patients according to their functional impairment. This scale is a useful tool for assessment of the effectiveness of different therapies and even prognosis. The lower the Karnofsky score, the worse the prognosis for most serious illnesses. Measurement of hematological indices was conducted with 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 fasting state.

Study data were analyzed using SPSS software version 11.5 for Windows. Analysis of variance (ANOVA) test was used for repeated measures, paired *t*-test was applied for comparison of quantitative variables (weight, appetite, hematological, and hepatic biochemical indices) and χ^2 was used for comparison of ratios and percentages.

Results

In this study, 60% of patients were male (18 men, 12 women) and mean age was 56.23 ± 12.10 years. Liver metastasis was secondary to different cancers (Table 1). Four patients withdrew from the study at the start. Of these 4 patients, 3 patients did not start the study or withdrew during the first week and one died during the first week of the study because of esophageal variceal hemorrhage (following esophageal cancer). The other 3 patients were lost to follow-up and did not use the drug although they were alive. Three patients withdrew during the 4th week of study and 4 withdrew in 8th week of study; of these 1 died (because of pulmonary emboli following breast cancer) and the others were lost to follow-up without any reaction to the drug.

The patients were monitored for drug side effects, changes in their hematological indices, and adverse events. Mild drug side effects were observed only in 3 cases (10%), including mild temporal headache (1 case) and mild epigastric pain (2 cases), which discontinued with dose reduction.

Patients' appetite improved significantly after first week of treatment ($P < .002$). Mean body weight of patients increased slightly, but not significantly, during the study period ($P > .05$; data not shown). Abdominal pain also improved significantly after the first week of study ($P < .001$).

Assessment of patients with Karnofsky Performance Scale showed a significant improvement in the patients' performance after 12 weeks of treatment, and mean Karnofsky performance score in patients surviving until the end of study increased from 48 ± 14.36 before beginning of drug use to 78.42 ± 15.37 after 12 weeks of treatment ($P < .001$; Figure 1).

Table 1. Cancer Types in the Patients Studied

Cancer Type	n
Colon cancer	17
Pancreatic adenocarcinoma	3
Hepatocellular carcinoma	3
Breast cancer	2
Leiomyosarcoma	1
Biliary duct adenocarcinoma	1
Gastric adenocarcinoma	1
Ovarian cancer	1
Esophageal adenocarcinoma	1

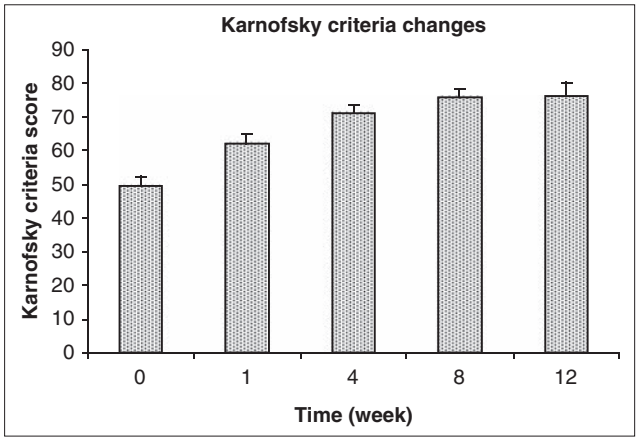

Figure 1. Changes in Karnofsky performance score of the patients during the study

Based on assessment of liver enzymes, the hepatic function of the patients improved significantly during the study (Table 2). As shown by paired *t*-test, there was a significant decrease in the level of hepatic enzymes during the study ($P < .05$).

No significant changes were observed in hematological parameters during the study period (Table 2) except for creatinine, which decreased significantly. A total of 90.4% of patients who did not withdraw from the study, survived until the end of study (3 months).

Discussion

This study showed anticancer effects of HESA-A, a herbal–marine compound, in patients with end-stage metastatic cancer. After 3 months of therapy, patients' functional impairment (according to the Karnofsky Performance Scale) improved significantly. Also, no significant adverse effect was reported during the study.

As the patients' appetite improved significantly after treatment, we predicted patients' weight gain but we did not observe any significant changes in body weight during the study; perhaps because of the short study period.

The lack of selectivity for tumor cells, which 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.

In an experimental model, it was shown that HESA-A could inhibit the growth of cancer cells (MDA-MB-46, Hep-2, and Hela), selectively and in a dose-dependent manner.[20] 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. These antitumor properties of HESA-A were confirmed in the preclinical phase of study.[18,20] HESA-A is not cytotoxic toward normal cell lines. This effect was also shown by an in vitro study.[20] A major consideration in this selective effect is the possible interaction with cellular DNA. Apoptotic effects of HESA-A may also have a major role in its anticancer properties.[14,21]

HESA-A is rich in trace elements. Se, Zn, Ni, and Ti are among the constituent elements of HESA-A, with antioxidant properties that have been studied.[22] The presence of these elements and antioxidant compounds in HESA-A may contribute to its anticancer effects.

Titanium has displayed notable anticancer effects in drug complexes. The anticancer effect of selenium in stopping neoplastic growth in rats has also been confirmed in another study.[15] Vanadium-containing compounds have exhibited anticancer properties and nickel has been shown to have antimitotic properties in vitro.[16,17] Thus, the antitumor effects of HESA-A may be because of the presence of these elements in its composition.

In previous and recent clinical trials, the efficacy and safety of HESA-A in the treatment of metastatic breast and colon cancers was also confirmed.[23,24]

In HESA-A toxicological studies, no biochemical, hematological, or histopathological signs of toxicity were observed.[13,18]

Small sample size, absence of control group, and no assessment of patients' quality of life are the main limitations of this study.

It appears that HESA-A is a useful and safe anticancer drug with selective effect, which may be applied in selected patients. However, further prospective controlled clinical trials with large sample size and longer follow-up period are warranted to better 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 as well as its unfavorable side effects.

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Table 2. Changes in Hematological and Biochemical Parameters in the Patients During the Study

Study Phase Parameter	Before Treatment, n = 30 (Mean ± SD)	After 3 Months of Treatment, n = 19 (Mean ± SD)	*P* Value
Hemoglobin (mg/dL)	11.22 ± 1.00	11.88 ± 0.78	.49
Uric acid (mg/dL)	4.08 ± 1.05	4.34 ± 0.87	.60
BUN (mg/dL)	15.83 ± 3.40	16.43 ± 2.69	.52
Cr (mg/dL)	1.06 ± 0.52	0.88 ± 0.16	.003[a]
SGOT (U/L)	72.55 ± 53.74	41.55 ± 18.05	.005[a]
SGPT (U/L)	61.55 ± 38.11	39.11 ± 11.99	.003[a]

NOTES: BUN = blood urea nitrogen; Cr = creatinine; SGOT = serum glutamic oxalacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
[a]$P < .05$ (significant).

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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