Original Paper

# First Clinical Data of a Natural Immunomodulator in Colorectal Cancer

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**ABSTRACT**

**Background/Aims:** MSC (trade-name AVEMAR®) is a *per os* applicable complex of multiple, biologically active molecules obtained from fermented wheat-germ extract. Preclinical studies suggest potent anti-metastatic activity and it has a favorable toxicity profile. It has been aimed in a pilot-scale, phase II clinical study to document whether or not MSC as a support to surgery or plus chemotherapy adds any therapeutic benefit compared to the same combination without MSC in colorectal cancer.

**Methodology**: From 1998 to June 1999, 18 control patients and 12 consecutive colorectal cancer patients respectively, were enrolled into this study. All patients underwent curative surgery. The control group (18 patients) received no other therapy or adjuvant chemotherapy alone. The MSC group (12 patients) received MSC alone or plus adjuvant chemotherapy. Until now, the median follow-up has been 9 months.

**Results:** Interim data of the study document that in the MSC group no new metastases, neither hepatic nor other, have occurred, so far. On the contrary, several new metastases have developed in the control group.

**Conclusions:** Orally administered MSC is a potent candidate to be regarded as a supportive therapy to surgery or plus chemotherapy for colorectal cancer patients.

## INTRODUCTION

MSC (trade-name AVEMAR®) is a *per os* applicable complex of multiple, biologically active molecules obtained from fermented wheat-germ extract. Preclinical studies suggest potent anti-metastatic activity and it has a favorable toxicity profile (1). Oral administration of MSC enhances blastic transformation of splenic lymphocytes in mice. The same treatment shortens the survival time of skin grafts in a co-isogenic mouse skin transplantation model, pointing to the immune-reconstructive effect of the preparation (2). A highly significant anti-metastatic effect of MSC has been observed in 3 metastasis models (Lewis lung carcinoma, B16 melanoma, HCR-25 human colon carcinoma xenograft) (3). Combination of MSC and 5-fluorouracil (5-FU) or dacarbazine (DTIC) exhibited a dramatically enhanced anti-metastatic effect in C38 mouse colon carcinoma and B16 mouse melanoma models (4). MSC synergistically enhanced the metastasis inhibitory effect of these anti-neoplastic agents and profoundly decreased the toxic side effects of the chemotherapy. Furthermore, MSC did not show any toxic effects in acute oral toxicity studies carried out under Good Laboratory Practice conditions (GLP) (5-7). In fact, MSC is available as an over-the-counter dietary supplement in many countries. It has been proposed that MSC should be used as a support in the therapy of malignant neoplasia and other diseases caused by or associated with immune disturbances. Henceforth, numerous phase II clinical trials of MSC have been started in patients with metastatic carcinoma.

In this paper, interim results of a still running, pilot-scale, phase II clinical trial of MSC as a supportive therapy to surgery or plus chemotherapy in the treatment of colorectal cancer patients will be presented.

## METHODOLOGY

From 1998 to June 1999, 18, control patients and 12 consecutive colorectal cancer patients respectively were enrolled into this study. All patients underwent curative surgery. The latter intervention included complete removal of the primary tumor within the colorectum along with adequate lymphadenectomy. In cases of colorectal cancer metastatic to the liver, indicated by preoperative investigation, resection of hepatic metastases were also carried out. At the time of enrollment, 1 patient of both groups has had inoperable hepatic metastases. Another patient from the MSC group had previously undergone both liver and lung resections due to multiorgan dissemination. The control group (18 patients; 11 men, 7 women; mean age 70 years; range: 58-78) received no other therapy or adjuvant chemotherapy alone. The MSC group (12 patients; 6 men, 6 women; mean age 64 years; range: 51-86) received MSC alone or plus adjuvant chemotherapy. Chemotherapy indicated fluorouracil-

**KEY WORDS:** Avemar; Fermented wheat-germ extract; Colorectal cancer; Metastasis; Phase II clinical trial; Pilot study; Combination therapy; Supportive therapy

**ABBREVIATIONS:** Computed Tomography (CT); Dacarbazine (DTIC); 5-Fluorouracil (5-FU); Magnetic Resonance Imaging (MRI); Good Laboratory Practice (GLP); European Organization for Reasearch and Treatment of Cancer (EORTC)

Hepato-Gastroenterology 2000; 47:393-395

based systemic chemotherapy regimens. One patient from each group has received postoperative localized radiation therapy, too. Particulars for the 2 groups are shown in **Table 1**. MSC has been administered daily throughout the study. Nine (9g) grams of MSC were given 1-2 times a day orally 30min before meals. MSC patients were randomly assigned to take MSC once or twice a day. Until now, the median follow-up has been 9 months (range: 6-11). Patients have been seen and examined at the 1st day, 1st, 4th, 8th and 10th month of the study. Physical examinations including assessment of performance status, (EORTC) European Organization for Reasearch and Treatment of Cancer, Quality of Life and laboratory evaluations, as well as ultrasonic studies, have been effectuated regularly, plus computed tomography (CT) and magnetic resonance imaging (MRI) when needed. The objective of the study is to document whether or not MSC as a support to surgery or plus adjuvant chemotherapy adds any therapeutic benefit compared to the same combination without MSC in colorectal cancer. Therapeutic benefit is assessed by time to progression and measuring quality of life. It has also been aimed to document if MSC is able to delay the occurrence of new metastases in adjuvant relapsed setting in colorectal cancer patients. In the following, facts concerning the latter are presented.

**TABLE 1 Group Characteristics: TNM Classification of Colorectal Tumors and Indication of Chemotherapy**

| T | N | M | Number of Patients MSC Group (12 patients) | Chemotherapy |
|---|---|---|---|---|
| X | X | 1 | 1 | n. a. |
| 3 | X | X | 1 | (a) |
| 3 | 1 | 0 | 1 | n. a. |
| 4 | 0 | 0 | 1 | (b) |
| 4 | X | 1 | 1 | (b) |
| 4 | 1 | 0 | 1 | (b) |
| 4 | 1 | 0 | 1 | n. a. |
| 4 | 2 | 0 | 1 | (c) |
| 4 | 2 | 0 | 2 | (a) |
| 4 | 2 | 1 | 1 | (a) |
| 4 | 2 | 1 | 1 | n. a. |
| **Control Group (18 patients)** | | | | |
| 2 | 0 | 0 | 1 | (b) |
| 2 | 0 | X | 1 | n. a. |
| 3 | 0 | 0 | 1 | (b) |
| 3 | 0 | 0 | 4 | n. a. |
| 3 | 0 | 0 | 1 | (c) |
| 3 | 1 | 0 | 1 | n. a. |
| 3 | 1 | 1 | 1 | n. a. |
| 4 | 0 | 0 | 1 | (b) |
| 4 | 0 | 0 | 2 | n. a. |
| 4 | X | 0 | 1 | (b) |
| 4 | 0 | X | 1 | n. a. |
| 4 | 2 | 0 | 3 | n. a. |

n.a.: Not applied; a: Single-agent 5-FU bolus infusion regimen; 5-FU 750mg/m$^2$ i.v. for 5 days; to be repeated 4 times on every 4th week (15); b: Continuous oral 5-FU prodrug (Ftorafur); 800mg/day for up to 15g of total intake (16); c: Protracted infusion of 5-FU plus radiation therapy ("NCI, March 1991 protocol" recommendation); 5-FU 500mg/m$^2$ i.v. for 3 days at weeks 1, 5, 9 and 5-FU 450mg/m$^2$ i.v. for 5 days at weeks 13, 17, 21; radiation, 45 Gy followed by boost 5.4 Gy in 3 fractions to the tumor bed, over 6 weeks (17-18).

## RESULTS

Until now, no new metastases, neither hepatic nor other, have developed in the MSC group. One patient (T4N2M0) with a history of recurrence has developed an inoperable relapsed tumor. However, he is in a good physical condition with good performance status. Four patients from the MSC group have already had metastases at the time of their enrollment into the study. One of the patients (TXNXM1) has inoperable hepatic metastases. Another has undergone liver resection. Another patient, before his enrollment into the study, had undergone both liver and lung resections due to multiorgan metastases. The 4th patient has had metastasis within the omentum. All of them are in good physical condition with good performance status. The same could be said about the other patients of the MSC group. Furthermore, no side effects concerning the administration of MSC have been reported.

The patient (T3N1M1) in the control group who had inoperable hepatic metastasis, has died. Another patient (T4N0MX) of the control group has developed multiple metastases, and is in a very serious condition. Two other patients (T3N0M0; T4N2M0) from the control group have also developed metastases and eventually died. The rest of the control patients are in good physical condition with good performance status.

## DISCUSSION

Colorectal cancer is the second leading cause of cancer related death in many countries including e.g., Hungary, Israel and the United States (8-10). Primary colorectal cancer may produce lymphogenic and hematogenic metastases. The hematogenic dissemination generally leads to hepatic metastasis with a median 5-year survival of only 7%. Disseminated colorectal cancer is considered as incurable (11). The natural history of patients with colorectal cancer metastatic to the liver is therefore exasperating (12). Among the monotherapeutic modalities for colorectal cancer patients suffering from liver metastases, surgery is still the most beneficial one (13). For these patients, combination of local or systemic adjuvant chemotherapy and surgical intervention may result in some additional improvement of their prognosis. There is however, a great bulk of evidence indicating that at the time of diagnosis most of the colorectal cancer patients have already harbored disseminated tumor cells or micrometastases which are not detectable by routine diagnostic procedures (14). In the large majority of patients, these hiding cells or cell populations will give rise to systemic metastases. Due to the presence of micrometastatic deposits, most of the solid neoplastic tumors of the colorectum must therefore be regarded as systemic disease. This concept may represent a strong indication for using systemic chemotherapy in the treatment of colorectal cancer patients in adjuvant/neoadjuvant setting. Colorectal carcinomas are however, primarily chemoresistant tumors. Systemic chemotherapy is furthermore, inseparably associated with several, severe side effects. Any medication or therapy which has no notable adverse effects and can display anti-metastatic support,

and/or may alleviate the toxic side effects of the chemotherapy, therefore deserves attention. According to previous preclinical data, and the interim but promising clinical results presented in this communication, orally administered MSC is a potent candidate to be regarded as a supportive therapy to surgery or plus adjuvant chemotherapy for colorectal cancer patients.

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