Phase I Trial of Methotrexate-Albumin in a Weekly Intravenous Bolus Regimen in Cancer Patients

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ABSTRACT

Methotrexate-albumin conjugate (MTX-HSA) is a novel human albumin-based prodrug conjugate of methotrexate (MTX). A low MTX loading rate provided optimal tumor targeting and therapeutic efficacy during preclinical testing. The objectives of this first Phase I study of MTX-HSA were to determine dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) in a weekly regimen. Seventeen cancer patients who were no longer amenable to standard treatment were enrolled and evaluable for DLT. Up to eight injections were performed in weekly intervals. Dose escalation was as follows: 20, 40, 50, and then 60 mg/m² MTX-HSA (based on the amount of MTX bound to albumin). Additional MTX-HSA courses were feasible in case of tumor response. DLT (mainly stomatitis, Common Toxicity Criteria grade 3) occurred, beginning at the 50 mg/m² dose level after repeated administrations; in one case, thrombocytopenia was dose-limiting. Two events of DLT occurred at the 60 mg/m² dose level within the first two administrations. Mild anemia, transaminitis, and one case of skin toxicity were found. No significant leukopenia, nausea, renal toxicity, or other toxicities were observed. MTX-HSA was well tolerated. Drug accumulation occurred on the weekly schedule. The half-life of the drug was estimated to be up to 3 weeks. Tumor responses were seen in three patients: (a) a partial response was seen in one patient with renal cell carcinoma (response duration, 30 months, ongoing); (b) a minor response was seen in one patient with pleural mesothelioma (response duration, 31 months, ongoing); and (c) a minor response was seen in one patient with renal cell carcinoma (response duration, 14 months until progression). Poststudy treatment was administered at 2–4-week intervals. No signs of toxicity or drug accumulation were seen. Altered pharmacological properties of MTX-HSA such as plasma half-life, tumor targeting, or intracellular metabolism might have contributed to these responses. The MTD for weekly administration was 4 × 50 mg/m² MTX-HSA during short-term treatment. A regimen with MTX-HSA injections of 50 mg/m² every 2 weeks was recommended for a further clinical Phase I study.

INTRODUCTION

MTX³ (amethopterin) was synthesized by Seeger et al. about 50 years ago (1). The antimitobolite MTX provided the first example of a drug-induced cancer cure by chemotherapy after administration to women suffering from metastatic choriocarcinoma (2). Since then, a broad range of single-agent cytostatic activity has been described, especially when MTX is given as a high-dose treatment counteracted by folinic acid rescue (3). Nowadays, a variety of MTX treatment modalities and promising new antifolates have evolved (4). MTX can be used in low-dose regimens without folinic acid rescue (30 mg/m² once a week or 50–100 mg/m² at 3–4 week intervals). Intermediate- or high-dose MTX treatment (100–1,500 or 8,000–12,000 mg/m² every 1–4 weeks) requires folinic acid rescue to curb toxic side effects such as severe stomatitis, gastrointestinal mucositis, or myelosuppression (5). After i.v. administration, MTX is rapidly removed from circulation by the kidneys (40% after 6 h and 90% after 24 h), causing nephrotoxicity in some instances. The remainder is metabolized to 7-hydroxy-MTX, mostly in the liver. The mean distribution half-lives range from 1.5–3.5 h, whereas the terminal half-life is about 8–15 h (6).

Consequently, the tumor exposition time of MTX is short, if tumor volume doubling times measured in weeks or months for human cancers are considered (7). Not only a short in vivo half-life of MTX impairs an optimal therapeutic effect, but also the high interstitial pressure of solid tumors, caused by a missing lymphatic drainage, results in low tumor accumulation rates for MTX, favoring drug disposition toward healthy tissue (8). To overcome these limitations, we searched for a macromolecular drug targeting system that would offer a longer circulating

³ The abbreviations used are: MTX, methotrexate; MTX-HSA, methotrexate-albumin conjugate; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; CTC, Common Toxicity Criteria; CT, computed tomography; EMIT, enzyme multiplied immunoassay technique.

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half-life of MTX and would increase the tumor uptake rate. These requirements are realized by albumin. It carries about 70% of the transportable nitrogen reserves available in blood (9). Recent experimental evidence suggested that albumin preferentially accumulated in tumors (10–12). Proliferating cells take up albumin by fluid-phase endocytosis. After lysosomal digestion, the derived amino acids serve as a source for nitrogen and energy in the tumor cell. Albumin catabolism by the tumor itself is responsible in part for the nitrogen transfer to the tumor (13). These favorable properties supported the choice of albumin as a drug carrier.

Throughout the last three decades, a variety of attempts have been made to use albumin as a drug carrier for MTX. To our knowledge, the experiments with MTX-HSA conjugates remained in the preclinical state. The discrepant molecular weights of MTX ($M_r \approx 454$) and albumin ($M_r \sim 67,000$) directed all efforts to improve the therapeutic efficacy of these conjugates by raising the molecular load from an initial value of about 10 mol of MTX conjugated per albumin molecule to MTX-HSA carrying 56 mol of MTX (14–18). Recent radiopharmacological experiments in tumor-bearing rats demonstrated that MTX-HSA bearing more than 3 mol of MTX was preferentially trapped by the liver. Optimal pharmacokinetic features were found for MTX-HSA with a loading rate of approximately 1 mol of MTX. The distribution pattern of these conjugates in healthy and tumor-bearing rats was indistinguishable from native albumin. High tumor accumulation rates for both albumin and the MTX-albumin conjugate were observed, exceeding 15% of the injected dose after 72 h in rat Walker-256 carcinoma (19, 20).

Antitumor activity of this MTX-albumin conjugate was shown in Walker-256 carcinoma in SD rats, in a prostatic adenocarcinoma Dunning (R-3327-Hi) in Copenhagen rats, and in a variety of human xenograft tumors in nude mice models (21–23). Preclinical toxicology screening in mice showed a favorable profile of MTX-HSA. Mucositis, stomatitis, shaggy fur, and diarrhea were typical side effects that were followed by signs of myelosuppression (predominant leukopenia) if the dose was stepped up. On the basis of these favorable properties, MTX-HSA was selected for further clinical development. We now report on the first Phase I study of MTX-HSA in cancer patients.

**MATERIALS AND METHODS**

**Patient Characteristics and Study Guidelines.** The trial was conducted under the guidance of the Phase I Study Group of the Association of Medical Oncology of the German Cancer Society and was sponsored by the German Cancer Research Center, Heidelberg. The objective of this study was to define the MTD of MTX-HSA and to record short-term, delayed, or late toxicity for a weekly administration regimen. Drug administration was monitored to determine steady-state conditions of the drug. All patients were required to have histologically proven cancer that was no longer amenable to standard treatment. Eligibility criteria were as follows: (a) performance status, WHO grades 0–3; (b) age, 18–75 years; (c) life expectancy, at least 3 months; (d) adequate bone marrow, liver, and renal function; (e) no chemotherapy or radiotherapy for at least 4 weeks; and (f) informed consent. Patients with brain metastases or with known contraindications for MTX treatment were excluded. The protocol was approved by the Ethics Committee of the University of Heidelberg, Germany. The study was performed according to the standard operating procedures of the Association of Medical Oncology Phase I/II Study Group (24).

Histories, physical examinations, full laboratory evaluation, and an electrocardiogram were performed at study entry and every 2 weeks during treatment. Blood counts were performed weekly. Extensive laboratory screening included testing for electrolytes, creatinine, urea, cholinesterase, bilirubin, albumin, serum electrophoresis, alanine aminotransferase, aspartate aminotransferase, $\gamma$-glutamyltranspeptidase, alkaline phosphatase, glucose, uric acid, blood lipids, Quick, a partial thromboplastin time, fibrinogen, and semiquantitative urine analysis. Radiological investigations comprised a chest X-ray, sonography, and CT or magnetic resonance imaging scans. Patient performance was classified from 0 to 4 according to the WHO scale. Treatment-related toxicity was graded according to the CTC checklist, which was adapted and published by the Phase I/II Study Group (24). Adverse drug reactions were defined as any adverse event whose relation to therapy was certain, probable, or possible. Improvements in disease had to persist for 4 weeks before being considered as a response. Initially, tumor response was checked every 4 weeks; during poststudy treatment, it was checked every 3 months. Duration of response was measured from the beginning of MTX-HSA treatment until the development of progression.

**Treatment.** MTX-HSA was provided in 50-ml vials (1 mg of MTX per ml of solution bound to 100 mg of HSA; molar loading rate, 1:3:1) by the German Cancer Research Center, Heidelberg. The drug was administered i.v. once a week. The initial dose was chosen according to the LD$_{10}$ [lethal dose (for 10% of the mice)] calculation from preclinical toxicology in mice. The MTD of MTX-HSA in mice was 50 mg MTX/kg body weight (LD$_{10}$) administered weekly for 4 weeks. Converted to body surface, the MTD corresponded to 20 mg MTX/m$^2$ bound to albumin (later referred to as 20 mg/m$^2$ MTX-HSA; Ref. 25). Dose levels were escalated from 20 mg/m$^2$ to 40 mg/m$^2$ and 60 mg/m$^2$ and then de-escalated to 50 mg/m$^2$. Three patients were treated at each dose level. In each group, at least eight injections (one injection/week) were intended. If no DLT was observed during the first three administrations, the next dose level was started. If an episode of DLT occurred, up to six patients were treated at that level. If DLT occurred in more than two of these patients, then accrual stopped. The MTD was defined as one dose level below that at which two of six patients developed DLT. An additional six patients were intended for confirmation of this dose level. After the Phase I study period of 8 weeks, treatment intervals could be prolonged in responding patients. DLT was defined according to CTC. Critical parameters were grade 3 toxicity for hematological parameters; coagulation parameters; stomatitis; diarrhea; gastritis; gastrointestinal tract ulcers; mucositis; diseases of the lung, kidneys, urinary tract, skin, eyes, and ears; and neurological or autoimmune disorders. CTC grade 4 toxicity was chosen for hepatic function, metabolic disorders, vascular diseases, loss of appetite, and alopecia. Toxicity for each patient was assessed every week.
Drug Monitoring of MTX-HSA. For pharmacokinetic analysis, blood samples were drawn before injections, 1 h after injection of MTX-HSA, 1 day after injection of MTX-HSA, and every 1 or 2 weeks during poststudy treatment. All samples were stored at $-20^\circ$C until processing. MTX-HSA concentrations were determined using a modified EMIT procedure (20, 26). The EMIT MTX test is a homogeneous enzyme immunoassay. Patient MTX competes with MTX conjugated to a bacterial glucose-6 phosphate dehydrogenase enzyme for common binding sites of a sheep antibody to MTX (27). The antibody reactive patients’ characteristics are listed in Table 1. Seventeen patients with various solid tumors were eligible. The median performance status was 1 according to the WHO scale. The number of courses administered is shown in Table 2. All 17 patients were evaluable for DLT within the first two consecutive courses; 13 patients received at least three courses, 12 patients received at least seven courses, and 8 patients received more than seven consecutive courses. One patient withdrew informed consent after two courses, and treatment was discontinued in two patients because of tumor-induced health deterioration after the second or third injection.

Nonhematological Toxicity

The data for nonhematological adverse drug reactions are shown in Table 3. Stomatitis was the major DLT. First signs (CTC grade 1) were seen in the 40 mg/m$^2$ group after six courses. It occurred with grade 3 intensity in the 50 and 60 mg/m$^2$ groups, beginning after four administrations in a patient treated with 50 mg/m$^2$ and after two or four courses in two patients treated with 60 mg/m$^2$. One female patient showed signs of skin toxicity with slight papulosquamous lesions on both forearms and legs (grade 3) after the first administration of 60 mg/m$^2$. This patient had a known history of 5-fluorouracil-induced skin toxicity. All DLT symptoms resolved within 7–14 days after treatment was stopped. Folinic acid rescue was not necessary. Further adverse drug reactions in these patients were intermittent nausea, diarrhea, constipation, and slight nose bleeding due to mucositis not exceeding CTC grade 1–2. Two patients complained of fatigue possibly related to the treatment. Among other adverse events not considered to be associated with treatment were single events of dyspnea, edema, thrombosis, and fever and one case of supraventricular tachyarrhythmia.

Hematological and Laboratory Toxicity

Hematological and laboratory adverse drug reactions are listed in Table 4. After six consecutive weekly administrations of 40 mg/m$^2$ MTX-HSA, thrombocytopenia with a nadir (19,000/μl) at day 10 (grade 4) was dose-limiting in one patient. No severe bleeding was seen, and normal values were reached within 15 days. Two patients in the 50 mg/m$^2$ dose level showed grade 2 thrombocytopenia after eight consecutive courses. No leukopenia was found, and in a single case, grade 1 granulopenia occurred. Single events of a relative lymphopenia were seen in some patients up to grade 3. Despite ongoing treatment, normal values were re-achieved. In some patients, intercurrent transaminitis (up to grade 3) and slight elevations of alkaline phosphatase occurred. One patient without liver metastases showed CTC grade 3 elevation of transaminases (alanine aminotransferase, 214 units/liter, aspartate aminotransferase, 140 units/liter) once after three administrations (50 mg/m$^2$ dose level), which resolved under ongoing treatment. In some patients, grade 2 or grade 3 transaminitis and hyperbilirubinemia.
binemia were associated with a rapid progression of liver metastases. Further adverse laboratory events (CTC grades 1–3) that were not considered to be associated with treatment included deviations of coagulation parameters, glucose, blood urea nitrogen, creatinine, bilirubin, alkaline phosphatase, transaminases, and electrolytes. Slight intercurrent increases of creatinine were found in two patients. One patient with a known history of choledocholithiasis showed a short episode of a grade 2 increase in amylase. Overall, MTX-HSA could be administered safely to outpatients. Allergic reactions or other acute toxic reactions did not occur, even in patients with tumor responses, each patient receiving more than 35 injections of MTX-HSA.

**Therapeutic Activity of MTX-HSA**

In 3 of 10 patients treated with 50 or 60 mg/m² MTX-HSA, tumor regressions were observed.

**Case I.** Minor tumor response was observed in a 69-year-old woman who suffered from a life-threatening solitary metastasis of renal carcinoma that had infiltrated the cervical spine, compressing the spinal chord despite radiation therapy. In this patient, therapy began with 60 mg/m² MTX-HSA. After four administrations of MTX-HSA, stomatitis (CTC grade 3) occurred, confined to the regions of the mouth adjacent to the target area of the previous radiotherapy to the cervical spine. Treatment was interrupted until complete recovery 3 weeks later, de-escalated, and continued with weekly injections of 40 mg/m². The neurological symptoms caused by tumor compression of the spinal chord disappeared. After another two injections, slight stomatitis (grade 2) reappeared. MTX-HSA treatment was continued, but intervals were prolonged to injections every second or third week. The patient received 28 injections with a cumulative dose of 2124 mg of MTX conjugated to HSA (152 mg MTX/month). A 30% tumor regression was documented by CT scans and lasted 14 months until tumor progression.

**Case II.** Tumor response was observed in a 61-year-old man who had developed a large cell pleural mesothelioma in March 1996. The tumor infiltrated the right pleura and the mediastinum. Tumor removal by decortication was not feasible.
Pleurodesis was unsuccessfully performed three times. The patient suffered from recurrent pleural effusions, and dyspnea worsened until April 1996. The patient was enrolled in the 50 mg/m² MTX-HSA group. At the end of the study treatment period, after eight administrations of MTX-HSA, stomatitis (grade 2) and thrombocytopenia (grade 2) were observed. Treatment was interrupted for 3 weeks until complete restitution and then continued with 50 mg/m² MTX-HSA at 2–4-week intervals. During week 24, slight stomatitis recurred, and treatment was paused again for 4 weeks and then resumed. Until September 1998, the patient had received 35 administrations of MTX-HSA (cumulative MTX dose, 3270 mg or 121 mg MTX/month). No significant toxicity was observed. Chest X-rays showed a continuing reduction in tumor burden of about 40%. Dyspnea had vanished during the study period. The patient reported well-being, and the MTX-HSA treatment was being continued (tumor response time, 31 months, ongoing).

Case III. Tumor response was also seen in a 63-year-old male patient who had undergone nephrectomy due to renal cell carcinoma in 1989. In 1993, he developed a local solitary lymph node metastasis that was surgically removed; other lymph node metastases reappeared and were no longer surgically amenable. Despite IFN treatment, tumor progression occurred. In June 1996, the patient presented with progressive disease (multiple pulmonary metastases and several intra-abdominal para-aortal metastases of up to 6 cm in diameter). After two injections of 60 mg/m², the treatment had to be paused due to cholangitis (known cholelithiasis) for 5 weeks. Treatment was resumed with weekly injections of 50 mg/m² MTX-HSA. After five administrations, treatment was paused due to stomatitis (grade 2). Since September 1996, therapy has been continued with 50 mg/m² MTX-HSA injections every 2–4 weeks. No toxicity was observed. CT scans showed a reduction of the pulmonary metastases and the intra-abdominal lymphomas of more than 80%. Until September 1998, 39 courses of MTX-HSA had been administered (cumulative MTX dose, 3430 mg; 123 mg MTX/month). At the time this article was completed, there had been no signs of tumor progression, the patient had reported well-being, and the MTX-HSA treatment was being continued (tumor response time, 30 months, ongoing).

Therapeutic Drug Level Monitoring

Typical MTX-HSA concentration curves are shown in Figs. 1 and 2 from two patients with tumor responses (see “Case II” and “Case III”). In Fig. 1, the plasma concentrations obtained during 16 courses of MTX-HSA are shown. Peak concentrations of 90 μmol/liter MTX-HSA were measured 1 h after the injection of 50 mg/m² MTX-HSA. Due to the prolonged half-life of MTX-HSA, the drug conjugate accumulated from a baseline value of 15 μmol/liter MTX-HSA to 40 μmol/liter MTX-HSA after eight injections. Due to side effects, treatment was paused for 3 weeks and resumed after the side effects had disappeared and the baseline MTX-HSA concentrations had dropped to 25 μmol/liter MTX-HSA. By injecting MTX-HSA every 2–3 weeks, steady-state conditions were achieved. After an additional six courses, slight side effects (stomatitis) recurred at baseline concentrations of about 30 μmol/liter MTX-HSA. To be on the safe side, the treatment was stopped until baseline concentrations had decreased to approximately 15 μmol/liter MTX-HSA. For further long-term treatment, the MTX-HSA concentrations were kept between 10 and 20 μmol/liter. In Fig. 2, MTX-HSA plasma concentrations of a patient with renal cancer are shown, including the first 15 injections over 36 weeks. Initially, the patient received two administrations of 60

![MTX-HSA concentration curves](https://example.com/fig1.png)
mg/m² MTX-HSA. Due to an episode of a cholangitis, treatment was interrupted and was later resumed with 50 mg/m² MTX-HSA in weekly courses. After five injections, MTX-HSA accumulated to 30 μmol/liter MTX-HSA. Grade 2 stomatitis was observed, and the treatment was paused. On weeks 27 and 28, the patient received injections of MTX-HSA, but only baseline concentrations were measured. After keeping the MTX-HSA concentrations between 10 and 20 μmol/liter, no major side effects of long-term MTX-HSA have been reported in this patient. The declines in plasma baseline concentration during treatment interruptions clearly showed that the half-lives of the MTX-HSA conjugate were close to 3 weeks. If administered in 2–3-week intervals, steady-state conditions were achieved during poststudy treatment.

DISCUSSION

This Phase I study demonstrated that the prodrug conjugate MTX-HSA could be safely administered to cancer patients. The conjugate comprises MTX, a cytostatic drug, and human albumin, a macromolecular carrier. The loading rate of albumin with MTX was kept low at a molar ratio of approximately 1:1.3. Preclinical studies had revealed that low loading rates were crucial for optimal tumor targeting. Only conjugates with a loading rate below 3:1 (MTX:HSA) enjoyed the same favorable distribution pattern and the long plasma half-lives of native albumin (19).

Toxicity Profile. Seventeen patients received weekly injections over a period of 2–8 weeks (a total of 102 courses) or until DLT. All injections were well tolerated, without signs of allergic reactions or a vascular leakage syndrome. Side effects of MTX-HSA observed in this study did not differ from the side effects commonly known from conventional MTX treatment. The predominant side effect was grade 1–3 stomatitis. If stomatitis grade 2 or grade 3 occurred in a patient, the treatment was paused. On weeks 27 and 28, the patient received injections of MTX-HSA, but only baseline concentrations were measured. After keeping the MTX-HSA concentrations between 10 and 20 μmol/liter, no major side effects of long-term MTX-HSA have been reported in this patient. The declines in plasma baseline concentration during treatment interruptions clearly showed that the half-lives of the MTX-HSA conjugate were close to 3 weeks. If administered in 2–3-week intervals, steady-state conditions were achieved during poststudy treatment.

MTD. The MTD was established for four courses of 50 mg/m² MTX-HSA administered at weekly intervals for short-term treatment. Due to drug accumulation, a weekly regimen is not suitable for long-term treatment. The administration of 50 mg/m² MTX-HSA every 2–4 weeks, achieving plasma concentrations between 10 and 20 μmol/liter, proved to be safe and effective, based on observation of the three responding patients.

Tumor Responses. Three tumor responses were seen, two (a minor response and a partial response) in patients with renal carcinoma and one (a minor response) in a patient suffering from pleural mesothelioma. Both tumor entities are known for their resistance to conventional chemotherapy (28, 29). A variety of hypotheses might apply, based on the information available on tumor pathophysiology and the pharmacology of conventional MTX, the MTX-albumin conjugate, and the carrier protein albumin. Tumor volume doubling times in man range from weeks to months, although the replication process at the cellular level is completed within a time interval of a few tens of hours in the majority of individual tumor cells. This discrepancy is brought about by tumor cell loss due to necrosis or apoptosis (7). In this setting, successful antimetabolite-based chemotherapy, which is only effective during the comparatively short S-phase of the cell cycle, will require a continuous presence to exert an optimal therapeutic impact on the tumor. In this respect, the pharmacokinetics of the prodrug MTX-HSA differ decisively from conventional MTX. The conjugate takes advantage of the long biological half-life of albumin in man (19 days), the role of albumin as a major source for tumor nitrogen, and, consequently, the accumulation of albumin in tumors. We were able to maintain MTX-HSA levels in two cases over more than 30 months, continuously providing the cytostatic drug conjugate in vivo over several tumor volume doubling times. On the basis of the injected dose of MTX-HSA (50 mg/m²), it can be estimated that an injection of 100 mg of MTX-HSA will include approximately 10 g of the carrier protein. The albumin pool in man was estimated to be 350 g (9). One injection of MTX-HSA will cover about 3% of the albumin pool; after repeated injections of MTX-HSA, one can expect a 5% share. Thus, about 1 of 20 albumin molecules might be tagged by MTX.

Conclusions. MTX-HSA is a novel chemotherapeutic prodrug conjugate. Phase I testing revealed an excellent toxicological profile, allowing outpatient treatment and maintaining a high quality of life status for all cancer patients. Altered pharmacological properties of this conjugate in terms of plasma half-life, tumor targeting, and intracellular metabolism might contribute to the tumor responses observed in two patients with
renal cancer and in one patient with pleural mesothelioma. MTX-HSA will be evaluated in additional Phase I and Phase II trials.

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