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Clinical Trials Summaries

Phase II Trial of Trimetrexate in Patients with Advanced Renal Cell Carcinoma

CORA N. STERNBERG, ALAN YAGODA, HOWARD SCHER, GEORGE BOSL, DAVID DERSHAW, KIM ROSADO, COLLETTE HOUSTON, RICHARD ROSENBLUTH, VINCENT VINCIGUERRA, BRUCE BOSELLI and the Clinical Community Oncology Program

Memorial Sloan-Kettering Cancer Center, Solid Tumor Service, 1275 *York Avenue, New York, NY* 10021, *U.S.A.*

INTRODUCTION

THE overall response rate to chemotherapeutic agents in patients with renal cell carcinoma (RCC) is 0–15%; only vinca alkaloids, nitrosoureas and interferons show marginal activity. Antifols such as methotrexate (MTX), triazinate (Baker's antifol) and 10-deaza-aminopterin (10-DAAM) have been evaluated [1]. TMTX, a 2,4-diaminoquinazalone, is one of a series of diaminoquinazoline folate antagonists developed to identify antifolates with a therapeutic index greater than MTX. Like MTX, TMTX is a potent inhibitor of dihydrofolate reductase (DHFR), which may offer an advantage over MTX in not requiring the reduced folate carrier protein for cell membrane transport, deletion or alteration of which has been implicated in MTX resistance. TMTX does not form polyglutamates, thought to contribute to MTX toxicity [2, 3]. TMTX has demonstrated activity against several murine tumors including the implanted B 16 melanoma, colon 26, L1210 and P388 leukemias, and s.c. implanted CDF1 mammary tumor, a spectrum somewhat different from MTX. In phase I trials, toxicity to TMTX revealed myelosuppression, mucositis, skin rash, diarrhea, liver and renal abnormalities [4–6]. A phase II trial was undertaken in an effort to define the efficacy of TMTX in patients with advanced RCC.

MATERIALS AND METHODS

Patients had advanced, surgically unresectable, bidimensionally measurable RCC, histologically confirmed at MSKCC with a KPS of ≥60% and a life expectancy of ≥6 wks, a WBC ≥3000 cells/mm^3; PLT ≥120,000 cell/mm^3, bilirubin ≤1.5 mg%, SGOT ≤2.0 × normal, BUN ≤25 mg/dl, and creatinine ≤1.5 mg/dl. All patients signed informed consent. Patients had no prior chemotherapy or irradiation within 3 weeks of therapy. TMTX, 10–12 mg/m^2 i.v. over 10 min daily for 5 consecutive days every 3 weeks was given. Patients with prior radiation received 8 mg/m^2 i.v. Patients had a CBC weekly, and repeat scans and X-rays every 3–6 weeks. For grade 0 or 1 toxicity in the previous course the dose was escalated 25%. For grade 3 toxicity, the dose was reduced by 50%.

Table 1. *Patient characteristics*

Total entered	14
Age (years)	
Median	57
Range	(49–71)
Karnofsky performance status	
Median	90%
Range	(60–100%)
Prior chemotherapy	1
No prior chemotherapy	14
Prior brain irradiation	2
Prior radical nephrectomy	9
Sites of disease	
Bidimensionally measurable	
Lung	10
Lymph nodes CTT	5
Renal mass	3
Soft tissue mass	2
Liver	1
Evaluable disease	
Osseous	3

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Address for reprints: Cora N. Sternberg, M.D., Via Aurelia, 559, 00165, Rome, Italy.

TMTX was held for creatinine of ≥2 mg/dl or bilirubin ≥2 mg%, or greater than 3 × increase in SGOT or SGPT, and until WBC ≥3,000 cells/mm^3; PLT ≥ 120,000 cells/mm^3. Two courses and 8 weeks survival were considered an adequate trial. Unequivocal PROG with dose-limiting toxicity, after five doses (one course) and 3 week survival was also considered evaluable.

RESULTS

Patient characteristics are found in Table 1. The median dosage was 10 mg/m^2 (range 8–15.5 mg/m^2); median number of cycles was 2 (range 1–9). Of 14 patients, one has a MR for 9+ months, one was stable for 4 months, and 12 had PROG. Myelosuppression was most marked in the initial two patients treated at 12 mg/m^2 (nadir counts of 700 and 800 cells/mm^3). Median WBC nadir was 3900 cells/mm^3 (600–6800), platelets 129,000 cells/mm^3 (51,000–422,000) and hemoglobin 10 g/dl (6.3–13.7). Skin rash was seen in two patients and nausea in three. These data suggest limited activity for TMTX in patients with advanced RCC. Although TMTX was well tolerated, primarily in the outpatient setting, at this dosage and schedule there is no role of TMTX in the treatment of advanced RCC.

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