Cancer Chemother Pharmacol (2002) 50: 151–154
DOI 10.1007/s00280-002-0470-2

ORIGINAL ARTICLE

**Steven C. Plaxe · John A. Blessing · George Olt
Nader Husseinzadah · Samuel S. Lentz · Koen DeGeest
Fidel A. Valea**

A phase II trial of pyrazoloacridine (PZA) in squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study

Received: 17 October 2001 / Accepted: 17 April 2002 / Published online: 5 July 2002

The following Gynecologic Oncology Group institutions participated in this study: Abington Memorial Hospital, Colorado Foundation for Medical Care, Hospital of the University of Pennsylvania, The Milton S. Hershey School of Medicine of the Pennsylvania State University, University of Cincinnati College of Medicine, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, Wake Forest University School of Medicine, University of California Medical Center at Irvine, Rush-Presbyterian-St. Lukes Medical Center, State University of New York at Stony Brook, Pennsylvania Hospital, Columbus Cancer Council, University of Massachusetts Medical Center, Fox Chase Cancer Center, University of Oklahoma Health Sciences Center, University of Virginia Health Science Center, University of Chicago, Thomas Jefferson University Hospital and Case Western Reserve University.

S.C. Plaxe (✉)
Department of Reproductive Medicine, Medical Center,
University of California, San Diego,
402 Dickinson Street, San Diego, CA 92103-8433, USA
Tel.: +1-619-5436905
Fax: +1-619-5433703

J.A. Blessing
Gynecologic Oncology Group,
Roswell Park Cancer Institute, Buffalo, NY 14263, USA

G. Olt
Department of Obstetrics and Gynecology,
Milton S. Hershey Medical Center/Pennsylvania State University
School of Medicine, Hershey, PA 17033, USA

N. Husseinzadah
Department of Obstetrics and Gynecology,
Division of Oncology, University of Cincinnati,
Cincinnati, OH 45267, USA

S.S. Lentz
Department of Obstetrics and Gynecology,
Section on Gynecologic Oncology,
Wake Forest University School of Medicine,
Winston-Salem, NC 27157, USA

K. DeGeest
Department of Gynecology Oncology,
Rush Medical College, Chicago, IL 60612, USA

F.A. Valea
Department of Obstetrics and Gynecology
and Reproductive Medicine,
State University of New York at Stony Brook,
Stony Brook, NY 11794, USA

Abstract *Purpose*: The Gynecologic Oncology Group performed a phase II study to determine the response rate to pyrazoloacridine (PZA) in patients with advanced, persistent or recurrent squamous carcinoma of the cervix. *Methods*: PZA was administered intravenously over 3 h every 3 weeks. A dose of 760 mg/m^2 was given to the first 11 patients and was reduced to 560 mg/m^2 for subsequent patients. The dose reduction was undertaken because of unexpected severe neutropenia among the initial patients. *Results*: Among 24 evaluable patients, 21 of whom had prior chemotherapy, there was one, brief, complete response (4.2%) and no partial responses. The major toxicity was neutropenia. *Conclusion*: PZA at the dose and schedule employed, has insignificant activity in this population.

Keywords PZA · Pyrazoloacridine · Cervical cancer

Introduction

Approximately 60% of patients with locally advanced squamous cell carcinoma of the cervix will have disease persistence or recurrence after local therapy [8]. In a series of phase II trials conducted by the Gynecologic Oncology Group (GOG) single-agent activity in squamous cervical cancer has been demonstrated for cisplatin, ifosfamide and dibromodulcitol [13, 14, 15]. These drugs, as well as bleomycin and paclitaxel, have been evaluated in combination in recent phase III studies [3, 6, 7], although none of the regimens have yet shown improved long-term survival compared to single-agent cisplatin. In view of the poor prognosis of patients with advanced or unresectable recurrent disease, new active agents are being sought.

Pyrazoloacridine (PZA, NSC 366140) is a 9-methoxy acridine compound selected for clinical development on the basis of several unusual properties observed during preclinical evaluation. Although the mechanism of action is unknown, acridine compounds cause cytotoxicity through DNA and RNA interactions. PZA acts as a

DNA intercalator [1, 2] and also inhibits RNA synthesis. PZA may inhibit both topoisomerase I and II [11] and is active against multidrug-resistant tumor cells [12]. Compared to other agents, it has demonstrated increased activity against solid tumor lines relative to leukemic tumor lines. It has also shown unusual activity against hypoxic cells and plateau-phase (noncycling) cells, which are not commonly targeted by other drugs.

With both 1- and 3-h infusions given every 3 weeks, the most common toxicities are emesis, leukopenia, anemia and neutropenia. Reversible neuromotor and neuropsychiatric disturbances have been seen with 1-h infusions [5], but are eliminated with a 3-h schedule [11]. Myelotoxicity increases with the 3-h schedule [11]. Responses in phase I trials have been reported in patients with colon, cervical and ovarian cancers [11]; however, no significant activity has been reported in pancreatic [18] or colorectal [17] carcinomas. A dose of 750 mg/m^2 administered every 21 days has been used, and tolerated, in phase II trials in pancreatic cancer [18], colorectal cancer [17], transitional cell carcinoma [4] and ovarian cancer [9], but lower doses have been prescribed in other populations. In a phase II study of patients with cisplatin-refractory germ cell tumors, 600 mg/m^2 was given every 3 weeks and 46% of the patients experienced grade 3 or 4 neutropenia [16]. In a GOG phase II trial in patients with endometrial cancer, all of whom had previously received chemotherapy and radiation, the initial starting dose of 750 mg/m^2 was reduced to 560 mg/m^2 because of an unacceptably high frequency of granulocytopenia among the first patients enrolled [10]. Neutropenia was a predominant toxicity in each of these trials [4, 9, 10, 11, 16, 17, 18].

The GOG initiated a phase II clinical trial to determine the response rate to PZA in patients with advanced, persistent or recurrent squamous cell carcinoma of the cervix and to describe the nature and degree of toxicity in this population. The phase II dose of 750 mg/m^2 given every 3 weeks appeared tolerable for most populations and was chosen as the initial starting dose for this investigation.

Material and methods

Women with advanced, persistent or recurrent squamous cell carcinoma of the cervix were enrolled on a GOG phase II study of PZA. All patients had disease progression after local treatment and were allowed only one prior chemotherapy regimen. Patients had measurable disease, GOG performance status of 2 or less, and adequate hematologic, hepatic and renal function. Patients with pre-existing neurologic toxicity were eligible; however, the toxicity was required to be limited to paresthesia and decreased vibratory sense without motor weakness. All patients were required to be able to function independently and be without delirium, confusion, suicidal ideation or untreated depression. Patients with another prior or concomitant malignancy, other than non-melanoma skin cancer were not eligible.

Written informed consent was obtained from all patients prior to entry on study fulfilling all institutional, state and federal regulations. The study was approved by the institutional review board of all participating institutions.

The initial starting dose of PZA was 750 mg/m^2 in 500 ml dextrose 5% in water over 3 h, but this was decreased to 560 mg/m^2 after the first 11 patients had been treated because of an unexpectedly high frequency of myelotoxicity. Patients were retreated every 3 weeks. All patients received antiemetics. Patients who received one or more courses of treatment and who survived at least 3 weeks were evaluable for response. Patients who received one or more courses were evaluable for toxicity.

Granulocytes $>1500/\mu l$, platelets $>100{,}000/\mu l$, creatinine ≤ 1.5 mg%, bilirubin ≤ 1.5 mg/dl and recovery of all other toxicities to GOG grade 1 or less were required for retreatment. If toxicity persisted, treatment delay to a maximum of 14 days was permitted to meet the above criteria. If toxicity had not resolved to permit treatment within 14 days from the planned treatment, the patient was removed from study.

Dose reductions to 75% and 50% and escalation to 125% of the starting dose were required based on tolerance of the prior course. One-level dose reduction was required for any of the following: febrile neutropenia or grade 4 neutropenia (absolute neutrophils $<500/\mu l$), platelet transfusion or grade 4 thrombocytopenia (platelets $<25{,}000/\mu l$) or nonhematologic toxicity of grade 2 or more (except nausea or vomiting). Two dose reductions were permitted for each patient. Myelosuppression was initially managed by dose delay and/or dose reduction without the use of G-CSF or other hematopoietic growth factors. At the discretion of the treating physician, management of recurrent myelosuppression with G-CSF, rather than a second dose reduction was permitted. One-level dose escalation was required if all of the following were met on the previous course: no treatment delay for recovery of toxicity, no hematologic toxicity of grade 2 or more, no nausea or vomiting of grade 3 or more and no other nonhematologic toxicity of grade 1 or more.

Patients were assessed prior to each course of treatment and disease measured only by scans was assessed before every second course of treatment. Treatment was continued until disease progression or the patient became unable to tolerate 50% of their original starting dose.

The GOG has tested numerous agents in phase II trials in this population and only six have demonstrated response rates in excess of 10%. The group has determined that novel agents with response rates less than 10% are unlikely to warrant further study and that those with response rates in excess of 30% will certainly be of great interest. Therefore, the present trial incorporated a two-stage sampling design with the intent of accruing approximately 25 patients during the initial stage. Three or fewer responses among the first 25 patients enrolled would indicate a response rate of less than 10% and further study would not be indicated. If four or more responses were observed among the first 25 patients enrolled, then an additional 15 patients would be accrued to allow more precise determination of the true response rate. The power of this study to detect a response rate of greater than 30% was 93%.

Results

Of 28 patients enrolled, 2 (7.1%) were ineligible (1 because of incorrect cell type and 1 because of failure to adequately demonstrate an invasive primary lesion) and 1 (3.6%) was eligible but was inevaluable because she was never treated with PZA. Of the 25 evaluable patients, 1 (4.2%) was evaluable for toxicity but not for response, and the remaining 24 (85.7%) were evaluable for both response and toxicity. Of the 25 patients enrolled who were documented to have invasive squamous carcinoma of the cervix, 15 (60%) had disease within a previously irradiated field, 6 (24%) had disease outside a previously irradiated field and 4 (16%) had lesions in both previously irradiated and unirradiated fields.

The median age of the patients was 47 years, with a range of 24 to 73 years. Five patients had a GOG performance status of 0, 12 had a performance status of 1, and 7 had a performance status of 2. All 24 patients had persistent or recurrent disease and had received previous radiation therapy; 21 had received prior chemotherapy. The median number of courses given was two, with a range of one to four.

Response

There was one complete response in a palpable left supraclavicular lymph node assessed by physical examination, and no partial responses among the first 24 evaluable patients. In the one complete responder, the site of progression after complete response was in the lung. The total response rate in this study was, therefore, 4.2%. The duration of the complete response rate was only 29 days. Six patients (25.0%) had stable disease; the remaining 17 evaluable patients (70.8%) had increasing disease.

Adverse effects

Adverse effects are summarized in Table 1. The predominant toxicities of PZA in this population were hematologic. Of 25 evaluable patients, 5 (20%) experienced grade 4 leukopenia, 5 (20%) had grade 4 neutropenia, 2 (10%) had grade 4 anemia and 1 (4%) had grade 4 thrombocytopenia. Three of the five patients who had grade 4 leukopenia received doses of 750 mg/m^2, and the other two were treated at 560 mg/m^2. The median nadir leukocyte count for the 14 patients with leukopenia was 1650/μl (range 100–3600/μl). There were no lethal adverse events.

Table 1. Adverse effects ($n = 25$)

Adverse effect	Grade				
	0	1	2	3	4
Leukopenia	5	3	3	9	5
Neutropenia	7	2	4	7	5
Thrombocytopenia	20	1	2	1	1
Anemia	7	2	6	8	2
Gastrointestinal	24	1	0	0	0
Nausea/vomiting	14	6	3	0	2
Genitourinary	24	0	1	0	0
Renal	19	3	1	2	0
Alopecia	23	2	0	0	0
Dermatologic	23	1	1	0	0
Alkaline phosphatase	22	0	2	1	0
Serum glutamate pyruvate transaminase	24	0	1	0	0
Neurotoxicity	19	4	1	1	0
Tinnitus	24	1	0	0	0
Fever	23	1	1	0	0
Hypomagnesemia	23	0	2	0	0
Hypokalemia	24	1	0	0	0
Hypercalcemia[a]	23	0	1	0	1
Pulmonary	24	1	0	0	0
Fatigue	24	0	0	1	0
Weight loss	24	1	0	0	0
Abdominal pain	24	0	0	0	1
Deep vein thrombosis	24	1	0	0	0
Leg swelling	23	2	0	0	0

[a]Attributed to patient's advanced cervical cancer

Conclusions

PZA at this dose and on this schedule was relatively well tolerated but it showed insignificant activity in patients with advanced, persistent or recurrent squamous carcinoma of the cervix. It is noteworthy that the original starting dose of 750 mg/m^2 was not tolerable in this patient population, most of whom had had prior radiation and chemotherapy. The reduced starting dose of 560 mg/m^2 appeared adequate since 20% of the population experienced grade 4 neutropenia.

Acknowledgements This study was supported by National Cancer Institute grants of the Gynecologic Oncology Group Administrative Office (CA 27469) and the Gynecologic Oncology Group Statistical Office (CA 37517).

References

1. Adjei AA, Charron M, Rowinsky EK, Svingen PA, Miller J, Reid JM, Leopold J, Ames MM, Kaufmann SH (1998) Effect of pyrazoloacridine (NSC 366140) on DNA topoisomerases I and II. Clin Cancer Res 4:683–691
2. Adjei AA (1999) Current status of pyrazoloacridine as an anticancer agent. Invest New Drugs 17:42–48
3. Bloss JD, Blessing JA, Behrens BC, Mannel RS, Rader JS, Sood AK, Markman M, Benda J (2002) Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 20:1832–1837
4. Dodd PM, McCaffrey JA, Mazumdar M, Icasaino E, Higgins G, Herr H, Bajorin D (2000) Phase II trial of pyrazoloacridine as second-line therapy for patients with unresectable or metastatic transitional cell carcinoma. Invest New Drugs 18:247–251
5. LoRusso P, Foster BJ, Poplin E, McCormick J, Kraut M, Flaherty L, Heilbrun LK, Valdivieso M, Baker L (1995) Phase I clinical trial of pyrazoloacridine (PD115934). Clin Cancer Res 1:1487–1493
6. Moore DH, McQuellon RP, Blessing JA, Thaler H, Benda J, Miller DS, Olt G, King S, Boggess J, Roccereto T (2001) A randomized phase III study of cisplatin versus cisplatin plus paclitaxel in stage IVb, recurrent or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study (abstract). Proc Am Soc Clin Oncol 20:801
7. Omura GA, Blessing JA, Vacarello L, Berman ML, Clarke-Pearson DL, Mutch D, Anderson B (1997) Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 15:165–171
8. Perez CA, Camel MH, Kuske RR, Kao MS, Galakatos A, Hederman MA, Powers WE (1986) Radiation alone in treatment of carcinoma of the uterine cervix: a 20 year experience. Gynecol Oncol 23:127–140
9. Plaxe SC, Blessing JA, Bookman MA, Creasman WT (2002) Phase II trial of pyrazoloacridine in recurrent platinum sensitive ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol 84:32–35

10. Plaxe SC, Blessing JA, Husseinzadeh N, Webster KD, Rader JS, Dunton CJ (2002) Phase II trial of pyrazoloacridine in patients with persistent or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 84:241–244
11. Rowinsky EK, Noe DA, Grochow LB, Sartorious SE, Bowling MK, Chen TL, Lubejko BG, Kaufmann SH, Donnhower RC (1995) Phase and pharmacologic studies of pyrazoloacridine, a novel DNA intercalating agent on single-dosing and multiple-dosing schedules. J Clin Oncol 13:1975–1984
12. Sebolt JS, Scavone SV, Pinter CD, Hamelehle KL, Von Hoff DD, Jackson RC (1987) Pyrazoloacridines, a new class of anticancer agents with selectivity against solid tumors in vitro. Cancer Res 47:4299–4304
13. Stehman FB, Blessing JA, McGehee R, Barrett RJ (1987) A phase II evaluation of mitolactol in patients with advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 7:1892–1895
14. Sutton GP, Blessing JA, Adcock L, Webster KD, DeEulis T (1989) Phase II study of ifosfamide and mesna in patients with previously treated carcinoma of the cervix: a Gynecologic Oncology Group study. Invest New Drugs 7:341–343
15. Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J (1981) Cisplatinum in the treatment of advanced or recurrent squamous carcinoma of the cervix. A phase II study of the Gynecologic Oncology Group. Cancer 48:899–903
16. Vuky J, McCaffrey J, Ginsberg M, Mariani T, Bajorin DF, Bosl GJ, Motzer RJ (2000) Phase II trial of pyrazoloacridine in patients wit cisplatin-refractory germ cell tumors. Invest New Drugs 18:265–267
17. Zalupski MM, Philip PA, LoRusso P, Shields AF (1997) Phase II study of pyrazoloacridine in patients with advanced colorectal carcinoma. Cancer Chemother Pharmacol 40:225–227
18. Zalupski MM, Shields AF, Philip PA, Kraut M, LoRusso P, Heilbrun LK, Vaitkevicius V (1998) Evaluation of pyrazoloacridine in patients with advanced pancreatic carcinoma. Invest New Drugs 16:93–96