TAS-108: A Novel Steroidal Antiestrogen

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ABSTRACT

TAS-108 is a novel steroidal antiestrogen compound that has a strong binding affinity to the estrogen receptor and, in preclinical studies, has antitumor activity against tamoxifen-resistant breast cancer cell lines. Its molecular mechanisms of actions are different from those of tamoxifen and fulvestrant. TAS-108 showed tissue-selective agonist activity in the bone and cardiovascular systems and, in preclinical and phase I studies, did not show any effect on the endometrium. In a phase I study, TAS-108 was well tolerated at doses ranging from 40 to 160 mg/d with no maximum tolerated dose. Toxicities included hot flashes, headache, and nausea and vomiting. The drug has linear pharmacokinetics. In the phase I study, there was evidence of biological antitumor activity, with stable disease noted in several patients. A phase II study is ongoing, and phase III studies are being planned with the drug.

INTRODUCTION

Tamoxifen is an antiestrogen with established clinical benefits for treatment of hormone receptor–positive advanced and early breast cancer (1). Tamoxifen also has been established as an effective agent in reducing the risk of hormone receptor–positive breast cancer in high-risk women (2, 3). The clinical use of tamoxifen is associated with increased risk of thromboembolic complications, uterine cancer, and, rarely, uterine sarcoma (4–7). Tamoxifen is a novel steroidal molecule [(7α)-21-[4-[(diethylami-no)methyl]-2-methoxyphenoxy]-7-methyl-19-norpregna-1,3,5(10)-trien-3-ol 2-hydroxy-1,2,3-propanetricarboxylate].

TAS-108 is a novel steroidal antiestrogen compound that has a strong binding affinity to the estrogen receptor and, in preclinical studies, has antitumor activity against tamoxifen-resistant breast cancer cell lines. Its molecular mechanisms of actions are different from those of tamoxifen and fulvestrant. TAS-108 showed tissue-selective agonist activity in the bone and cardiovascular systems and, in preclinical and phase I studies, did not show any effect on the endometrium. In a phase I study, TAS-108 was well tolerated at doses ranging from 40 to 160 mg/d with no maximum tolerated dose. Toxicities included hot flashes, headache, and nausea and vomiting. The drug has linear pharmacokinetics. In the phase I study, there was evidence of biological antitumor activity, with stable disease noted in several patients. A phase II study is ongoing, and phase III studies are being planned with the drug.

PRECLINICAL FINDINGS

In experimental systems, this drug is metabolized by four major pathways: conjugation of 3-hydroxy group, steroid ring hydroxylation, and N-oxidation resulting in N-oxide and N-deethylated forms. TAS-108 is metabolized to deethylated-TAS-108 mainly by CYP3A4 in human liver. Orally administered, TAS-108 and its metabolite deethylated-TAS-108 are distributed in tumor tissue at a significantly higher concentration than in serum. After p.o. administration of C-TAS-108 in rats bearing 7,12-dimethylbenz(a)anthrazene–induced mammary tumors, tissue distribution (tumor and uterus) of TAS-108 and deethylated-TAS-108 was high; tissue distribution of TAS-108-COOH was comparable with or lower than in the plasma; and TAS-108-N-oxide was barely distributed to the tissue.

In animal models, this drug has stronger or better antitumor activity than tamoxifen or fulvestrant and inhibits the growth of tamoxifen-resistant tumors (11–13). Animal model findings also suggest that this agent avoids the bone density loss associated with other antiestrogens (14). In animal toxicology studies, there was no serious toxicity observed, except for decreased body weight and decreased food consumption at high doses. There was no effect on the endometrial proliferation on the uterus, and no changes in ophthalmic examinations or coagulation variables were observed in rats and dogs. This drug was judged to be nonmutagenic in Salmonella/Escherichia coli and mouse lymphoma mutagenicity assays and also in micronucleus test using female mice.

CLINICAL EXPERIENCE

Ascending single-dose studies in normal healthy volunteers were carried out. Levels of TAS-108 in plasma were below the limitation of quantification in most subjects at the 10 and 20 mg dose levels. However, at the 40 mg dose level, the drug was detected in three of the five subjects. TAS-108 was readily absorbed following p.o. administration of 80, 120, and 160 mg doses, with a mean Cmax of 2.55, 5.16, and 7.61 ng/mL, respectively, increased in a dose-dependent manner (15). The drug levels steadily declined in a monoexponential manner, with overall half-life values ranging from 3.04 to 4.43 hours in the fasting group. Administration of 120 mg TAS-108 after a high-fat meal markedly increased the bioavailability. The mean Cmax and AUC0-∞ values obtained after a high-fat breakfast were 9.37 ng/mL and 63.3 ng × h/mL and 182% and 146% of the fasted value, respectively, although there was no apparent effect of the high-fat meal on half-life (3.43 ± 1.08 hours). These results suggested the administration of TAS-108 within 30 minutes after breakfast would be preferred. In healthy volunteers in the single-dose studies, no dose-dependent increase in adverse events was observed. The adverse events included mild nausea, arthralgia, muscle cramp, and moderate back and limb pain.

CLINICAL DATA: PHASE I STUDY

Based on the encouraging preclinical data and safety profile in experimental animal system and single-dose human studies, a phase I study was carried out at M.D. Anderson Cancer Center to evaluate safety of TAS-108 and also to determine its pharmacokinetics. The patient population consisted of postmenopausal women who had metastatic breast cancer that was documented to be hormone receptor positive. All patients had


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failed prior chemotherapy and endocrine therapy. These patients were required to have evidence of progressive disease after two or more prior systemic antitumor therapies, including at least one endocrine therapy. In this open-label nonrandomized dose-finding study of TAS-108, five different doses were evaluated sequentially: 40, 60, 80, 120, and 160 mg/doses. A minimum of three patients were enrolled on each dose level with once daily p.o. administration. If there were no drug-related grade 3 or higher toxicities in the first 14 days of the treatment, escalation to the next dose was started in the next three patients. If grade 3 or higher drug-related toxicity was observed in one of the three patients, three more patients were planned to be enrolled at the same dose level. The maximum tolerated dose of TAS-108 was predefined as one dose level below the dose at which two or more of the first three patients or a total of six patients experience grade 3 or higher drug-related toxicities. For pharmacokinetic studies, blood samples were collected at 2, 4, 6, 8, 10, 12, 14, and 24 hours after the first dose on day 1. Blood samples were also collected at days 15 and 28 before the dose of TAS-108 and on day 28 at 6 and 12 hours after the drug administration. TAS-108 and deethylated-TAS-108 plasma concentrations were analyzed using noncompartmental techniques.

The details of this phase I study have been published recently (16, 17). Most of the 16 patients enrolled in the study were heavily pretreated, and the majority had received three or more chemotherapies (62.5%) and three or more endocrine therapies (75%) before starting TAS-108. The safety profile of the drug was favorable. Adverse effects included hot flashes, nausea, or vomiting, which were mostly grade 1 to 2; one patient experienced grade 3 nausea. Other adverse effects included sweating, headache, and dizziness. One patient while on study experienced seizures; however, this patient was receiving other medications known to lower the seizure threshold. Transvaginal ultrasound studies were done in eight patients who had not undergone hysterectomy; ultrasound measurements of endometrial thickness at baseline and then at 4 to 12 weeks post-treatment showed no difference between the baseline and post-treatment thickness, suggesting that TAS-108 had no effect on the endometrial lining. This drug also had no effect on liver function, thyroid function, serum cholesterol, or serum electrolytes.

Pharmacokinetics

The drug was rapidly absorbed and reached $T_{\text{max}}$ at 2.7 to 5.3 hours post-dose. The concentration time profile showed a multiphasic elimination process. Mean terminal half-life range from 8.0 to 10.7 hours in an interval of 12 to 24 hours post-dose. $C_{\text{max}}$ ranged from 2.8 to 21.0 ng/mL and AUC$_{0.5}$ from 15.1 to 148.7 ng $\times$ h/mL. This showed a linear correlation with the dose. There was no unusual accumulation of the drug following multiple days of dosing. In one patient, plasma and tumor concentration were compared and the tumor concentration was found to be higher than the plasma concentration as observed in preclinical animal studies.

Tumor Response

In this heavily pretreated population, no patient achieved complete or partial response. Eight patients had stable disease for periods ranging from 11 to 60 weeks while on this drug. Of those, one patient maintained stable disease for 33 weeks, and another patient had stable disease for a total of 60 weeks on TAS-108. Eight patients had progressive disease.

DISCUSSION

TAS-108 is an novel steroidal antiestrogen compound, which in preclinical studies did not show any effect on the endometrium. The phase I study with this drug studied doses ranging from 40 to 160 mg/d. In this phase I study, the drug was well tolerated, and at the doses studied, there was no maximum tolerated dose. Adverse effects were mild and included hot flashes, headache, nausea, and vomiting. The incidence of these adverse effects was not related to the dose or duration of exposure. In this study, after exposure of this drug, there was no change in the endometrial thickness, providing clinical evidence that TAS-108 has no effect on the endometrial lining (i.e., no agonistic effect on the uterus). Although no clinical partial or complete responses were observed, a few patients experienced stable disease, suggesting the drug has antitumor activity in a heavily pretreated patient population. Currently, a multi-institutional phase II study is under way to define the optimal dose of the drug for a phase III clinical trial. If this drug shows a favorable therapeutic index, it may have a role not only in postmenopausal but also in premenopausal women with breast cancer.

OPEN DISCUSSION

Dr. Steven Come: In surveying the overall experience, it seems that response rates following aromatase inhibitors are low with all agents. Would there be any concern that conducting phase II studies this far down the line after AI exposure might result in discarding agents that would be effective if given earlier?

Dr. Aman Buzdar: Your point is very valid, but in fact we are having difficulty finding these patients, because most women who come to the major cancer treatment centers have been already treated with a number of endocrine agents. So, even to have patients who have been pretreated with only AI and tamoxifen is difficult.

Dr. Kent Osborne: With targeted therapies, such as TAS-108, that look promising in preclinical models, we ought to take them directly into the neoadjuvant setting. These can be brief 2- or 3-week studies that address questions like: Does it hit the target? Does it induce apoptosis? Does it stimulate MAP kinase or not? These studies can be done with a very short interval between diagnosis and definitive surgery and then the surgery provides the treatment biopsy.

Dr. Stephen Johnston: That was how the very first clinical studies on fulvestrant were done—just 7 days of treatment presurgery—which defined very nicely the effects on down-regulating ER and switching off Ki-67.

Dr. Come: How about the first-line metastatic setting with biopsying pre- and post-treatment?

Dr. Osborne: You can’t get the tissue, that’s one problem. Then, consider the relative responses to aromatase inhibitors or tamoxifen between adjuvant therapy and metastatic disease defined as a 1-cm lesion in the bone. With just a 1-cm lesion in the bone or the liver, the patient is incurable. Yet, when we use those drugs in the adjuvant setting, half the patients are cured.
That tells us that we can target the estrogen receptor in primary breast cancer with micrometastases and eradicate the tumor. In the metastatic situation, so many other redundant pathways are activated, hypoxia and stress pathways, all aimed at keeping the tumor cell alive, that it’s a wonder we see any response to tamoxifen or single-agent targeted therapy in that situation.

Dr. Buzdar: I think the neoadjuvant model is a very good suggestion, but the issue is whether we can go into that setting without knowing if the drug has any antitumor activity. I think at least you have to do a limited phase II study.

Dr. Osborne: Perhaps not for a 2- to 3-week treatment when definitive, essentially curative therapy is not being withheld. You just have to know it’s safe and that you have a biologic rationale and good preclinical data.

Dr. Johnston: The other question I have is where would we see this new drug, or a drug like this, coming in. In the advanced breast cancer setting, the development of the SERMs has been incredibly difficult. They possibly will have a role in the prevention setting because they won’t have the agonist effects of tamoxifen. Given that the AIs have leapfrogged in and taken over, to me an antiestrogen is either going to be a safer version of tamoxifen, where tamoxifen will still have a role, or else it is a different class of drug that can come in as a post AI therapy. People are now investigating whether fulvestrant has such a niche because it actually down-regulates and eliminates estrogen receptors. Looking at the structure, I have been wondering how different TAS-108 is from fulvestrant.

Dr. Osborne: It looks like fulvestrant.

Dr. Johnston: Yes, but does it actually down-regulate ER and has it got activity in tamoxifen-resistant models? If yes, then it would be an orally active version of fulvestrant, which would suggest post AI development does make sense clinically.

Dr. Per Lønning: All of us agree that early disease is an interesting setting to study new drugs. On the other hand, the very late setting is also interesting because that was where we learned the lesson that the steroidal and nonsteroidal aromatase inhibitors lack clinical cross resistance, which obviously told us that there must be a difference in the way they work in the tumor.

REFERENCES

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