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ORIGINAL ARTICLE

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Phase II trial and pharmacokinetic evaluation of cytosine arabinoside for leptomeningeal metastases from breast cancer

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Abstract *Purpose*: To determine the efficacy and pharmacokinetics of intraventricular cytosine arabinoside (Ara-C) as front-line treatment for leptomeningeal metastases from breast cancer. *Methods*: Ten patients newly diagnosed with leptomeningeal metastases (LMM) from breast cancer were treated with 100 mg intraventricular cytosine arabinoside (IVT Ara-C) via an Ommaya reservoir. Treatment was administered three times a week for 2 weeks, then once a week for 4 weeks, and then once every 6 weeks for four cycles to responding patients. Nine patients were evaluable clinically, and seven patients underwent testing to determine the pharmacokinetic profile of Ara-C in the cerebrospinal fluid (CSF). *Results*: Two patients had partial responses lasting 9 and 40 weeks, respectively. Two other patients had stable disease. The median survival duration was 30 weeks (range: 5–58 weeks). Seven patients died from LMM. Acute toxic effects associated with IVT Ara-C included meningismus, nausea, vomiting, and myelosuppression. The median peak Ara-C level in CSF was 16.69 ± 6.30 mM (SD). The half life for elimination was 1.45 ± 0.61 h (SD) There was no drug accumulation between courses. Neuropsychological evaluations were completed in eight patients, six (75%) of whom had preexisting cognitive deficits. Their condition generally improved over the course of treatment until the LMM progressed. No neurotoxic side effects of IVT Ara-C were observed in the two patients who had normal baseline cognitive assessments. *Conclusions*: IVT Ara-C at this dose and schedule has minimal activity as initial treatment for LMM from breast cancer despite achievement of high peak levels of the drug in the cerebrospinal fluid. A liposomal Ara-C formulation is currently under investigation.

Key words Breast neoplasms · Meningeal neoplasms · Cytosine arabinoside · Treatment

Introduction

Leptomeningeal metastases (LMM) is a serious but uncommon complication of solid tumors. Breast cancer is the most common epithelial malignancy associated with metastases to the meninges [11, 12, 13]. Results of an autopsy study of 1044 patients suggested that meningeal metastases may occur in as many as 18% of patients with metastatic breast cancer [23]. However, most of these patients were asymptomatic, and only about 5% developed clinically detectable LMM. It has been suggested that improved control of systemic disease with more aggressive chemotherapy may lead to improved survival rates and increasing rates of LMM [20].

Only a few cytotoxic drugs have been found to be suitable for administration into the cerebrospinal fluid (CSF). These include methotrexate, thiotepa, hydrocortisone, and cytosine arabinoside (Ara-C). Intraventricular (IVT) or intrathecal (IT) chemotherapy combined with radiotherapy to sites of bulky disease has prolonged median survival to 6 months in the best series

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[18, 19, 21, 23] and occasional long-term survivors are seen [10, 20, 22]. Methotrexate is the most commonly used chemotherapy in this setting; however, methotrexate may cause leukoencephalopathy, especially when administered with cranial radiotherapy [14, 15, 16]. There is no standard salvage therapy for patients who experience relapse, disease progression, or toxic effects requiring discontinuation of methotrexate.

Most of the patients we have treated with methotrexate or radiotherapy followed by Ara-C had no response. Only occasionally do we encounter a patient who has a long-lasting complete response to these treatments. However, Ara-C has not been fully evaluated as initial treatment for LMM from breast cancer. This report describes a phase II clinical study and pharmacokinetic evaluation of IVT Ara-C as front-line treatment for LMM from breast cancer.

Patients and methods

Patients

Eligible patients had LMM from breast cancer documented by the presence of malignant cells in the CSF. Patients had to have a functioning Ommaya reservoir, no prior IVT or IT chemotherapy, a life expectancy of >6 weeks, a Zubrod performance status of <3 [25], an absolute granulocyte count of $\geq 1500/mm^3$, and a platelet count of $\geq 100{,}000/mm^3$. All patients signed an informed consent document and were registered with the institution's Central Data Management office. Subjects were accrued from the existing population of metastatic breast cancer patients at The University of Texas M. D. Anderson Cancer Center or from among the patients referred to us after initial diagnosis of LMM.

Treatment

The planned schedule of treatment was Ara-C 100 mg IVT via an Ommaya reservoir three times a week (Monday, Wednesday, and Friday) for 2 weeks, then once a week for 4 weeks, and then once every 6 weeks for four cycles for responding patients. Radiotherapy was given if the disease progressed or remained unchanged after 2 weeks. Initial radiotherapy was given to untreated patients only for serious cranial nerve palsies, cerebral dysfunction, or cauda equina symptoms.

Monitoring and response determination

Neurological examination and CSF analysis for cytology, protein, glucose, carcinoembryonic antigen (CEA), and complete blood cell count were performed before each cycle of treatment. Neurocognitive tests were performed before the study, after 3 weeks of treatment, at removal from the study, and if a change in mental status occurred. These tests assessed the patient's ability to stay attentive, frontal lobe executive functioning, memory, reasoning, and visual-spatial functioning. CT or MRI of the brain was repeated every 6 weeks.

Complete central nervous system remission was defined as the disappearance of malignant cells from the CSF as determined by cytology studies and by differential count with Wright's stain; normalization of CSF cell count, glucose level and protein level; and improvement in neurological status lasting at least 4 weeks. Partial central nervous system response was defined as disappearance of malignant cells from CSF for less than 4 weeks or improvement in neurological status. Treatment failure was defined as lack of a partial remission after 6 weeks of treatment or if progressive disease occurred after 3 weeks of treatment. Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria [1].

Pharmacokinetics

The Ara-C levels in the CSF were measured before each treatment (baseline) and at 15 min; 30 min; and 2, 3, 5, 7, 24, and 48 h after Ara-C injection. CSF was collected from the Ommaya reservoir into heparinized tubes containing 0.5 mmol of tetrahydrouridine to prevent in vitro catabolism of Ara-C to uracil arabinoside by cytidine deaminase and refrigerated in ice water. Specimens were kept frozen at -20 °C until analyzed. Ara-C was measured by high-pressure liquid chromatography as previously described for gemcitabine and adapted without modification for Ara-C [5].

Results

Between June 1986 and December 1990 a total of 42 patients with LMM from breast cancer were seen at The University of Texas M. D. Anderson Cancer Center. Only ten of these patients fulfilled the criteria for treatment on the study and consented to the protocol. Nine of the patients were evaluable. The one inevaluable patient had seizures that developed 48 h after her first dose of Ara-C. Evaluation revealed that her serum sodium concentration was 117 mEq/l. Ara-C was discontinued, and she received IVT methotrexate. Table 1 shows the pretreatment characteristics of the nine evaluable patients. The majority were young, had estrogen receptor negative tumors, and had visceral extracranial metastases. In three patients, the histology of the primary breast tumor was lobular carcinoma. LMM was not the initial site of relapse in any of the patients. In seven patients,

Table 1 Patient characteristics at diagnosis of LMM

Characteristic	Value
Median age in years	49 (range: 32–72)
Histologic subtype	
Lobular	3
Infiltrating ductal	6
Estrogen receptor status (*n*)	
Positive	2
Negative	3
Unknown	4
Median time from diagnosis of systemic metastases to LMM (months)	12 (range: 0.5–32)
Median time from diagnosis of primary cancer to systemic disease (months)	26 (range: 3–135)
Dominant extracranial disease site	
None	2
Bone	1
Viscera	6
Status of systemic disease at diagnosis of LMM	
Complete response	2
Partial response	4
Progressive disease	3
Median no. of prior chemotherapy treatments	1 (range: 1–3)

the initial relapse was systemic metastases. Four of these patients responded to systemic treatment, and in three patients, systemic disease had progressed by the time LMM was diagnosed. In two patients, a solitary brain parenchymal metastasis developed, which was irradiated and resected. These two patients had no evidence of systemic disease. All patients had received at least one (range: 1–3) systemic chemotherapy regimen before the diagnosis of LMM.

The primary area of central nervous system involvement was the spine in two patients, the cranial nerves in one patient, the brain in four patients, the cranial nerves and brain in one patient, and all three areas in one. Table 2 shows the CSF findings at diagnosis. The opening pressure was elevated in five of the six patients in whom it was measured. Malignant cells were detected by cytology in only five of the nine patients at the time of diagnosis. In three others, the subsequent cytologic evaluation showed malignant cells during the course of treatment. In the other patient, the CSF cytology was never malignant, although on MRI, the classic appearance of enhancement in the basal cisterns and upper cervical cord was evident. A median of 11 doses of Ara-C were administered (range: 5–20 doses). Prior to IVT treatment, two patients had received radiation to the cauda equina region for rapidly progressive disease. Three patients continued to receive systemic chemotherapy during their IVT therapy. The chemotherapeutic agents used were 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). Four patients received IVT treatment alone.

Cognitive function was assessed in eight patients. Six of the eight patients (75%) had evidence of cognitive deficits prior to being treated with IVT Ara-C. The deficits observed varied from patient to patient, as expected, because of the multifocal nature of LMM and the effects of previous therapy. The two patients who had normal cognitive function prior to treatment also had normal assessments during their therapy.

Responses and survival

In two patients, a partial response was achieved lasting 9 and 40 weeks, respectively (response rate 22%; 95% confidence interval, 3%–60%). Two patients had stable disease, and the other patients had progressive disease. The median overall survival duration was 25 weeks (range: 5–57 weeks). The two partial responders survived 14 and 57 weeks, respectively. The two patients with stable disease survived for 30 and 36 weeks, respectively, and received salvage IVT methotrexate and thiotepa. The two patients who received radiation therapy prior to IVT Ara-C did not respond to Ara-C therapy. All but two patients died from the LMM; these two died from systemic disease. Of the patients who died from LMM, two had no systemic disease.

With regard to cognitive function, two of the six patients with preexisting cognitive impairments deteriorated significantly. Two other patients improved significantly, and the remaining two had transient deterioration and subsequently improved over the course of therapy.

Table 2 CSF findings at time of LMM diagnosis in nine patients. *CEA* carcinoembryonic antigen, *NA* not applicable

Characteristic	Median value	Range
Opening pressure, mm H_2O (n = 6 pts)	19	9–30
Glucose level, mg/dl	75	53–96
Protein level, mg/dl	26	< 10–77
Cytology		
Negative	4	NA
Positive	5	NA
Cell count/mm^3	100	13–100
% malignant cells	2	0–52
CEA level, ng/dl	< 1.5	< 1.5–4.8

Toxic effects

Only one patient (a partial responder) had meningismus, which occurred after 8 months of treatment. Of the four patients who did not receive cauda equina irradiation or systemic chemotherapy, three had myelosuppression (grade 2 in two patients, grade 3 in one patient). Two patients had nausea and vomiting, grade 1 and 2, respectively, which occurred only during one cycle of treatment. Three patients continued to receive systemic FAC chemotherapy during their IVT therapy. These patients experienced grade 2 nausea and vomiting during 5–7 days after the chemotherapy was administered, alopecia and grade 2 neutropenia. One of them developed grade 1 thrombocytopenia.

CSF pharmacokinetics

The CSF pharmacokinetic study conducted in seven patients showed that the mean peak Ara-C concentration in the CSF was 16.69 ± 6.30 mM (SD). There was no drug accumulation between courses. Ara-C was eliminated by deamination to uracil arabinoside with monophasic kinetics characterized by a half life of 1.45 ± 0.61 h (SD). The median concentration of Ara-C in the CSF 6 h after bolus infusion was 0.77 ± 0.53 mM (SD). Plasma levels of Ara-C were assessed in two patients and there was no evidence of Ara-C in plasma at a lower limit of detection of 50 μM by reversed-phase HPLC. The CEA spinal fluid levels were measured in nine patients at the time of LMM diagnosis (Table 2). The median spinal fluid CEA level was < 1.5 ng/dl (range: < 1.5–4.8). In this group of patients there was no apparent benefit of measuring spinal fluid CEA levels.

Discussion

Despite limitations of sample size, the results of this study (22% partial responses) appear inferior to the best

reported results (60% partial response) of the use of IT or IVT methotrexate for treatment of LMM [21, 23]. However, in the studies using methotrexate, all patients received radiotherapy. In our study, radiotherapy was used only for serious symptoms or rapidly progressive disease. The median survival duration of our patients is not different from that of other patients treated with IT or IVT methotrexate.

The CSF pharmacokinetic study showed that the mean peak Ara-C level in the CSF was 16.69 ± 6.30 mM (SD), and the average of the Ara-C concentration at 6 h was 0.77 ± 0.53 mM. These are very high concentrations of Ara-C, but they are comparable with those found after IVT administration as reported by Zimm and colleagues [24]. Results of tissue-culture experiments have indicated that Ara-C concentrations as low as 0.4 μM may have antineoplastic activity [4]. Hence, this study showed limited efficacy for IVT Ara-C as initial treatment for LMM in this schedule, despite achievement of high peak levels of Ara-C in the CSF. Is this result a function of intrinsic drug efficacy, dose schedule, or both? Systemically administered Ara-C is not known to be effective in the treatment of solid tumors. Feldman and associates [2] reported no responses to high doses of intravenous Ara-C given to patients with refractory breast cancer. A report by Fulton and colleagues [3] about the use of IT Ara-C as treatment for LMM yielded two widely differing results with regard to different dose schedules. The schedule-dependent efficacy of Ara-C has been established in experimental studies [9]; better results are obtained with continuous exposure as compared with bolus dosing.

Although the association between LMM and lobular breast cancer is substantial (three of nine patients), the prevalence of lobular carcinoma in this small series does not approach the 90% figure previously reported [6, 17]. The proportion of new patients with stage I through III invasive lobular breast cancer seen in our institution was 4.15% during this same period. Further evaluation of the other 32 patients with LMM who did not participate in the protocol, however, revealed that only seven had lobular histology. Whereas it is possible that some patients with lobular histology who came to our institution early in their disease were lost to follow-up and subsequently developed LMM, it is unlikely that we would not have detected more cases with LMM. Thus, we cannot confirm the increased incidence of LMM in patients who have the lobular histologic variant.

This small group of patients also illustrates the variable natural history of this disease. Although the median survival of patients who do not respond to treatment is short, one of the nonresponders survived for 26 weeks without any salvage therapy. Conversely, one of the partial responders survived for only 13 weeks from the time of diagnosis.

Our study serially evaluated higher cortical functioning by neurocognitive assessment. The advantage of neurocognitive assessment is that it detects changes in higher cortical functioning, which is easily missed by routine clinical assessment. However, it does not distinguish between changes caused by the disease and those caused by the treatment. In general, our results suggest that Ara-C would likely improve the cognitive functioning of patients with cognitive deficits secondary to LMM and who had evidence of stable or improved disease on treatment. Deterioration of cognitive functioning was more likely related to disease progression. Ara-C appeared to have no adverse neurotoxic side effects in individuals with normal cognitive function.

The main limitation of our study was the small sample size. The accrual rate was slow: only ten patients were treated during the 3.5-year study duration. This represents about one-fourth of all patients with LMM seen during that same period at our institution; however, many patients were excluded because of poor performance status from advanced systemic disease. This is not surprising because LMM is usually a late-occurring complication. Three of the patients received concomitant systemic chemotherapy and IVT Ara-C therapy. The toxicity observed could be explained by the administration of FAC chemotherapy alone. Because of the small sample size it is not possible to make any conclusions regarding the potential effect of systemic therapy on the patients' CNS disease.

In conclusion, the IVT Ara-C dose and schedule assessed in our study shows no apparent advantage over IVT methotrexate as initial treatment for LMM. However, Ara-C is a cell-cycle-specific antimetabolite, and the CSF concentrations achieved may be insufficient for biological activity. The antitumor efficacy of Ara-C is schedule-dependent, and it is possible that a more prolonged exposure of LMM to Ara-C might improve the results. Because continuous administration of the drug via an Ommaya reservoir is impractical and increases the risk for infection, a slow-release depot preparation of Ara-C, such as liposomal delivery, would be preferred [7, 8]. The Food and Drug Administration has recently approved liposomal-encapsulated cytarabine (DTC 101) for patients with non-Hodgkin's lymphoma and LMM. A multicentric clinical trial of DTC-101 is currently ongoing as treatment for neoplastic meningitis in patients with breast cancer and other solid tumors. Preliminary data indicate that DTC 101 is as effective as free Ara-C. The liposomal formulation can be administered every 2 weeks, and it has been suggested that this approach would be more convenient for patients with LMM.

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