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The combined use of radiation therapy and lonidamine in the treatment of brain metastases

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Summary

Lonidamine is an indazole carboxylic acid that has been shown to be synergistic with radiotherapy (RT) in tissue culture and animal models. Clinical experience has shown that lonidamine is well-tolerated, and appears to potentiate the activity of conventional chemotherapy in the treatment of brain metastases. A prospective randomized trial was undertaken to evaluate the use of lonidamine in combination with RT in the treatment of brain metastases. All patients received 3000 cGy of whole brain radiotherapy (WBRT). Fifty eight patients were enrolled; 31 received lonidamine plus WBRT and 27 received WBRT alone. There was no significant difference in response rate or survival between the treatment groups. Lonidamine blood levels were measured in 30 of the 31 patients who received the drug, and were therapeutic ($\geq 15\ \mu g/ml$) in 50%. Survival and response rate were unaffected by the presence or absence of a therapeutic lonidamine level. The most common side-effects of lonidamine were myalgia, testicular pain, anorexia, and ototoxicity; however, only 2 patients had to discontinue the drug because of intolerable myalgias. No serious organ toxicity or myelosuppression was observed.

Introduction

Brain metastases are a common complication of systemic cancer occuring in 15% of patients with a malignancy [1, 2]. They cause significant morbidity and contribute to mortality. Whole brain radiotherapy (WBRT) is the mainstay of treatment, offering effective palliation in most cases but rarely cure; median survival with WBRT is only 4–6 months [3]. Attempts to vary fractionation schedule and total dose of WBRT have not improved efficacy [4]. Radiosensitizers have been used in the hope of enhancing RT effect, but results with hypoxic cell sensitizers, such as metronidazole, have been disappointing [5, 6].

Lonidamine is an agent which interferes with cellular energy metabolism, and in tissue culture has demonstrated promise as a chemotherapeutic agent [7, 8]. Combined therapy with lonidamine and radiotherapy (RT) produces prolongation of local tumor control in animal models [9, 10]. Improved local control and increased survival was seen in patients with head and neck cancer and non-small cell lung carcinoma treated with lonidamine plus RT compared to RT alone [11–13]. Lonidamine appears to potentiate the activity of systemic chemotherapy in the treatment of brain metastases, but has not been tried in combination with WBRT, the most effective primary treatment of metastatic brain tumors [14]. Because the interac-

tion between lonidamine and RT is different from that of electronaffinic radiosensitizers, we undertook a randomized prospective study to determine whether the addition of lonidamine to WBRT can improve the response rate of patients with brain metastases.

Methods

All patients with a histologically confirmed cancer and brain metastases documented on CT scan were eligible. No patient had prior WBRT. At the time of diagnosis, all patients were treated with dexamethasone, usually 16 mg/day, but occasionally higher doses were necessary to control symptoms. Prior to randomization patients were stratified by primary tumor type, (i.e.; non-small cell lung carcinoma, breast carcinoma, melanoma and other), and by Karnofsky performance status, (i.e.; 50–70% and 80–100%).

Patients were randomly assigned to receive WBRT alone or WBRT plus lonidamine. All patients received WBRT at a dose of 300 cGy × 10 fractions for a total of 3000 cGy over 12–14 days through bilaterally opposed ports. Patients were continued on corticosteroids throughout RT, and were subsequently tapered as tolerated. Lonidamine (supplied by Angelini Pharmaceuticals Inc.) was administered as a single oral dose 1–2 hours prior to each RT treatment. The daily lonidamine dose was 430 mg/M^2/day; however, in order to minimize side effects from the drug, this dose was attained by gradual escalation over 5 days before the start of WBRT. The drug was continued for 1 week after completion of WBRT in all patients, and indefinitely at a dose of 300 mg/M^2/day in patients enrolled after January 1, 1986 (48% of study patients). Chronic lonidamine dosing was introduced half-way through the study because laboratory and preliminary clinical data suggested an improved response rate with long-term administration [9, 13].

CT scans were obtained prior to WBRT and monthly following the completion of treatment. Response was determined exclusively by changes on the contrast-enhanced CT scan. Patients were considered to have responded to treatment when there was a 50% or greater decrease in the size of the lesions, and they were on a stable or decreasing dose of corticosteroids. Those with less than a 50% decrease of the tumors were considered to be non-responders; the term progressive disease represented a 25% increase in the size of the initial lesions or appearance of new lesions. The 'best response' was determined for each patient; it was observed on the first post-WBRT CT scan for all patients except 3; 2 had a best response on the second follow-up CT scan and 1 patient on the third.

Lonidamine blood levels were determined for each patient receiving the drug after they reached the maximal dosage. A blood sample was drawn 1–2 hours after a lonidamine dose to document the effective concentration at the time of RT treatments. The serum lonidamine assays were performed according to the method developed by Besner *et al.* [15]. The therapeutic concentration was $\geq 15\ \mu g/ml$. Lonidamine toxicity was determined using a scale from 0–4 (zero = no toxicity, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening and 4F = drug-related death).

When cause could be determined, death was attributed to either neurologic or systemic disease. A neurologic death was considered to have occurred when a patient, with stable systemic disease, suffered an acute fatal intracranial event, such as hemorrhage or herniation, or had expanding intracranial masses or progressive leptomeningeal tumor. Patients with severe neurologic disability who died of intercurrent complications resulting from their disability (i.e.; pneumonia, pulmonary embolism) were also considered neurologic deaths. Patients who died with progressive systemic disease in the face of a stable or improving neurologic status were considered to have died systemic deaths. If there was a combination of progressive systemic and neurologic disease contributing to death, the death was considered neurologic. The development of a metabolic encephalopathy in the setting of otherwise stable or improving neurologic disease did not constitute a neurologic cause of death.

An evaluable patient was one who survived 6 or

more weeks from diagnosis of brain metastases and had at least one post-WBRT CT scan. Some patients who received lonidamine but did not survive for 6 weeks or who had to discontinue the drug because of toxicity were evaluable only for lonidamine toxicity but not for efficacy.

Of the enrolled patients, 16 received systemic therapy concommitant with or following treatment of their brain metastases; 15 patients received chemotherapy and 1, hormonal treatment. A systemic response to these treatments was seen in only 3 patients. Regression of cerebral metastases in response to systemic chemo- or hormonal therapy in the absence of a systemic response is distinctly unusual. Consequently, the brain metastases of the 13 systemic non-responders were evaluated with the rest of the study population. One patient with breast cancer received chemotherapy and had a systemic response to this treatment; however, her best response to cranial RT was observed on her first post-WBRT CT scan prior to the chemotherapy and is therefore included with the study population. Two other patients with a systemic response to chemotherapy were responders to WBRT; neither received lonidamine. Analysis of the data including and excluding these patients was identical, and therefore, they remained in the final analysis recognizing that the systemic chemotherapy may have contributed to their cerebral response.

Survival curves were drawn using the Kaplan-Meier product limit method [16]. The Pearson chi-square test was used for contingency table analyses.

Results

From January 1985 through January 1987, 58 patients were enrolled in the study; 27 received WBRT alone and 31 received WBRT plus lonidamine (WBRT + LON). There was no significant difference in age, sex, performance status, primary tumor type or percentage of evaluable patients between the 2 groups (Table 1). Of the 7 inevaluable patients in the WBRT group, 4 died from progression of systemic disease and 3 died from progressive neurologic disease before the first post-WBRT

Table 1. Patient characteristics

	WBRT (n = 27)	WBRT & LON (n = 31)
Sex		
M	10 (37%)	19 (61%)
F	17 (63%)	12 (39%)
Age		
Median	60	57
Range	(27–74)	(34–76)
Performance status (Karnofsky)		
50–70	14 (52%)	14(45%)
80–100	13 (48%)	17 (55%)
Patient status		
Evaluable	20 (74%)	19 (61%)
Toxicity alone	–	12 (39%)
Not Evaluable	7 (26%)	–
Histology		
Melanoma	8 (30%)	9 (29%)
Lung	9 (3%)	11 (35%)
Breast	4 (15%)	4 (13%)
* Other	6 (22%)	7 (23%)

* Other
WBRT – small cell lung carcinoma (3), renal (1), thyroid (1), adenocarcinoma unknown primary (1).
WBRT & Lonidamine – renal (3), small cell lung carcinoma (2), colon (1), thyroid (1).

CT scan could be obtained. Twelve patients could not be evaluated for efficacy in the WBRT + LON group, but all were evaluable for potential drug toxicity. Nine died from progressive systemic disease; 5 died prior to obtaining a follow-up CT scan, 2 had to stop the lonidamine because of toxicity, 1 patient refused to continue the drug and 1 died prior to completion of WBRT. Two other patients died from progressive neurologic disease; 1 patient received the wrong dose of cranial irradiation and was a protocol violation, the other died before a follow-up CT scan could be obtained. One patient was found dead at home from an unknown cause less than a month from entry onto the study.

There was no significant difference in response rate between treatment groups (Table 2); only 4 patients had a complete response, and all received WBRT alone. Survival was unaffected by the addition of lonidamine to WBRT. Median survival was actually longer for the WBRT group, 165 days, compared to the WBRT + LON group, 120 days, but this was not significant ($p = 0.42$). The proportion of patients who died a neurologic death was the same in both treatment groups. The presence of active systemic disease at the time of diagnosis of the brain metastases did not adversely influence survival. Survival was identical for those with disease limited to the brain and those with systemic disease plus brain metastases.

Because the addition of lonidamine had no impact upon survival, we added the evaluable patients of both treatment groups together to assess any potential difference in response rate or survival related to primary tumor type; however, the number of patients in each histologic subtype proved too small for meaningful analysis.

Lonidamine plasma levels were determined for 30 of the 31 patients who received the drug. Fifteen patients (50%) had subtherapeutic levels, and 15 achieved levels of 15 μg/ml or greater. Of the 19 evaluable patients who received lonidamine, 10 had therapeutic levels at 1–2 hours after ingestion. Survival was not significantly different in patients with therapeutic levels (median = 101 days) compared to those with subtherapeutic lonidamine levels (median = 138 days).

Table 2. Response rate in evaluable patients

	WBRT (n = 20)	WBRT + LON (n = 19)	Significance
Responders	11 (55%)	7 (37%)	NS

All patients who received lonidamine were evaluable for potential drug-related toxicity. The mean nadir platelet count was $225 \times 10^3/mm^3$ (range: $10–493 \times 10^3/mm^3$). Three patients had platelet counts below $100 \times 10^3/mm^3$; 1 had bone marrow involvement by tumor and 2 reached nadir during terminal sepsis. The mean nadir white blood cell count (WBC) was $8.3 \times 10^3/mm^3$ (range: $0.8–22.0 \times 10^3/mm^3$). Three patients had WBC below $2.0 \times 10^3/mm^3$; 1 had tumor in his bone marrow and 2 others received systemic chemotherapy, 1 of whom also received pelvic RT. No hepatic, pulmonary, cardiac or renal toxicity was seen.

The most common side-effects from lonidamine were myalgia (68%), testicular pain (42% of men), anorexia and ototoxicity (26% each), malaise/fatigue (26%) and nausea/vomitting (19%) (Table 3). Furthermore, there was no clear relationship between lonidamine level and maximal toxicity experienced by the patients. 27% of those with levels below 15 μg/ml had 3+ toxicity compared to 20% with levels ≥ 15 μg/ml. Of the 2 patients who had to discontinue lonidamine because of toxicity, 1 had a level of 6.0 μg/ml and the other had a plasma level of 45 μg/ml. Patients enrolled after January 1, 1986 and randomized to receive WBRT + LON were scheduled to receive the drug at a reduced dosage (300 mg/M^2/day) indefinitely. Fifteen of the 31 patients (48%) who took lonidamine were continued on the drug chronically. There was no difference in the incidence or degree of toxicity between the 2 groups except for ototoxicity which was more frequent (36%, 5/14) in those receiving chronic dosage compared to the acutely dosed patients (18%, 3/17), but not more severe. Most patients receiving chronic lonidamine eventually developed constitutional symptoms, i.e.; anorexia, malaise and fatigue, after completion of treatment for their brain metastases. The drug was discontinued in an effort to eliminate potential toxicity as the cause of these problems, but most patients did not improve when

the lonidamine was stopped. However, lonidamine was not reintroduced once it was discontinued, and consequently long-term maintenance on the drug was never achieved.

No acute or subacute radiation-related neurotoxicity was observed in either treatment group. One patient who received lonidamine and WBRT developed a subacute dementia accompanied by ataxia and urinary incontinence; this progressive syndrome began 6 months after completion of RT and initially occurred in the absence of a cerebral relapse from his metastasis. His dementing illness was attributed to radiation damage, perhaps exacerbated by the lonidamine; however, the patient subsequently developed recurrent brain metastasis and died a neurologic death 13.6 months after WBRT. Unfortunately an autopsy was not obtained. The potential synergy of lonidamine with WBRT may have contributed to this patient's dementia, but this is speculative. Furthermore, few patients were at risk for the late toxicities of cranial irradiation since only 12 patients (21%) survived for 6 months and 4 (7%) survived 1 year. Consequently, no comparison was possible between the treatment groups.

Discussion

Lonidamine is an indazole carboxylic acid which interferes with cellular energy metabolism at the mitochondrial level [7, 8]. Its activity requires mitochondria in a state of high oxidative capacity. Only a fraction of tumor cells have mitochondria in this state at any given time, and therefore, lonidamine-induced metabolic impairments alone are not likely to cause significant inhibition of tumor growth. In fact, lonidamine as a single agent has minimal tumoricidal activity [17–19]. Hyperthermia, radiation and some chemotherapeutic agents can induce cellular susceptibility to lonidamine, making them vulnerable to the drug's energy-depleting function. In addition, a tumor's capacity to repair potentially lethal damage (PLD) caused by RT, heat or chemotherapy may define or contribute to its relative resistance to this treatment. Lonidamine is thought to interfere with PLD repair mechanisms, an energy requiring process, when combined with these other therapies [9, 10, 20]. Furthermore, PLD repair is inhibited at clinically relevant doses of lonidamine [10, 20]. These mechanisms may explain the apparent synergy of lonidamine with conventional antineoplastic treatments [9–14].

Table 3. Lonidamine toxicity

Degree of toxicity Highest grade, per course, per patient (31 patients)	1	2	3	4	%
Anorexia	4	1	3	–	26
Fatigue/malaise	1	3	4	–	26
Myalgia	13	5	3	–	68
Nausea/vomiting	2	2	2	–	19
Photosensitivity	2	–	–	–	6
Testicular pain	5	2	1	–	42 (8/19 men)
Ototoxicity	8	–	–	–	26
Skin	–	4	–	–	13
Keratitis	1	–	–	–	3
Constipation	1	–	–	–	3

A prospective clinical trial combining lonidamine with carmustine (BCNU) and procarbazine in the treatment of brain metastases was strongly suggestive of an improved response rate, duration and enhanced survival in patients receiving lonidamine with chemotherapy compared to chemotherapy alone although statistical analysis was not applied [14]. A pilot study and a subsequent randomized prospective study of lonidamine and RT in head and neck cancer and non-small cell lung cancer suggested enhanced efficacy of the RT when combined with lonidamine [11–13]. While our present data are limited by the small number of patients, it seems clear that the addition of lonidamine to WBRT offers no advantage to WBRT alone. Lonidamine did not improve the response rate or survival of patients taking the drug. The lack of an effect could not be attributed to subtherapeutic lonidamine levels since response rate and survival were identical in those with serum levels $\geq 15\ \mu g/ml$ and those with levels below this accepted standard.

All patients who received lonidamine could be evaluated for potential drug toxicity. The majority had no serious side-effects. No enhanced radiation-

related neurotoxicity could be attributed to lonidamine although patient survival was too short to evaluate long term effects from the combined treatment. Only 2 patients had to discontinue the drug during the course of WBRT because of intolerable myalgias. However, 68% of patients did experience myalgia despite the concurrent administration of high dose corticosteroids for management of their neurologic symptoms; this incidence is comparable to that reported by other investigators for patients not routinely placed on corticosteroids. There was no serious organ toxicity in any patient. In particular, no significant hematologic toxicity was observed; we believe the few low WBC or platelet counts observed during treatment with lonidamine were a consequence of the systemic malignancy (e.g. tumor infiltrating the bone marrow) or its treatment (e.g., chemotherapy) since severe myelosuppression has not been reported previously for this drug. The absence of significant myelosuppressive toxicity makes lonidamine an attractive drug to use with conventional chemotherapeutic agents in the treatment of systemic malignancies where it may prove more effective.

While WBRT is the most important therapeutic modality for brain metastases, radiation enhancing drugs of varying mechanisms have not improved upon results with WBRT alone [5, 6]. This is not unexpected in view of the fact that such drugs effectively increase the dose of RT administered, and that increasing the dose of RT has not improved survival or response rate in brain metastases [4]. Although the preliminary results combining lonidamine and RT in head and neck and lung cancer are encouraging, the administered RT dose in those studies was 5600 cGy or greater [11–13]; high RT doses may be necessary to derive synergy with lonidamine, but are detrimental to brain. A variety of efforts to augment WBRT have failed to advance our conventional treatment of brain metastases. While WBRT remains the cornerstone of treatment, future progress for this difficult clinical problem will require novel approaches and development of new therapeutic strategies.

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