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ORIGINAL ARTICLE – CANCER RESEARCH

Safety of pioglitazone during and after radiation therapy in patients with brain tumors: a phase I clinical trial

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Abstract

Introduction Radiation-induced cognitive decline (RICD) is a late effect of radiotherapy (RT) occurring in 30–50% of irradiated brain tumor survivors. In preclinical models, pioglitazone prevents RICD but there are little safety data on its use in non-diabetic patients. We conducted a dose-escalation trial to determine the safety of pioglitazone taken during and after brain irradiation.

Methods We enrolled patients > 18 years old with primary or metastatic brain tumors slated to receive at least 10 treatments of RT (≤ 3 Gy per fraction). We evaluated the safety of pioglitazone at 22.5 mg and 45 mg with a dose-escalation phase and dose-expansion phase. Pioglitazone was taken daily during RT and for 6 months after.

Results 18 patients with a mean age of 54 were enrolled between 2010 and 2014. 14 patients had metastatic brain tumors and were treated with whole brain RT. Four patients had primary brain tumors and received partial brain RT and concurrent chemotherapy. No DLTs were identified. In the dose-escalation phase, there were only three instances of grade ≥ 3 toxicity: one instance of neuropathy in a patient receiving 22.5 mg, one instance of fatigue in a patient receiving 22.5 mg and one instance of dizziness in a patient receiving 45 mg. The attribution in each of these cases was considered "possible." In the dose-expansion phase, nine patients received 45 mg and there was only one grade 3 toxicity (fatigue) possibly attributable to pioglitazone.

Conclusion Pioglitazone was well tolerated by brain tumor patients undergoing RT. 45 mg is a safe dose to use in future efficacy trials.

Keywords Radiation-induced cognitive decline · Pioglitazone · Neuroprotective

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Introduction

Radiotherapy (RT) is an integral component of treatment for primary and metastatic brain tumors. Radiation-induced cognitive decline (RICD) is a late effect of radiotherapy (RT) occurring in 30–50% of irradiated brain tumor survivors (Greene-Schloesser et al. 2012; Meyers et al. 2004). Factors that influence the likelihood and severity of radiation-induced cognitive dysfunction include the total dose, dose per fraction, the volume of brain irradiated, age at the time of radiotherapy, and prior or concurrent chemotherapy (Aoyama et al. 2006; Brown et al. 2003, 2016; Chang et al. 2009; Correa et al. 2009; Douw et al. 2009; Gondi et al. 2014; Klein et al. 2002; Schultheiss et al. 1995).

Microvascular damage, demyelination, direct damage to neurons and supportive brain parenchymal cells, stem cell depletion, and changes in the brain microenvironment have all been reported as components of radiation-induced brain injury (RIBI) which is the histopathologic correlate of RICD (Andrews et al. 2017; Gualtierotti et al. 2017; Hanbury et al. 2015; Monje et al. 2007; Price et al. 2001; Raber et al. 2004). Recent evidence indicates chronic oxidative stress and persistent neuro-inflammation after RT plays a key role in RIBI (Andrews et al. 2017; Monje et al. 2002; Robbins and Zhao 2004; Yoritsune et al. 2014). Inflammation-associated histologic findings include diffuse microglial activation, microglial aggregation at sites of necrosis, and mononuclear perivascular cuffing.

Identifying effective interventions to prevent or mitigate RICD has been challenging. For patients with established cognitive decline after RT, memantine, donepezil, methylphenidate, and *Ginkgo biloba* have all been tried as mitigating pharmacologic strategies with varying levels of success (Attia et al. 2012; Brown et al. 2013; Butler et al. 2007; Shaw et al. 2006). Pharmacologic radioprotection to prevent RICD is of great interest but has been less studied. Ramipril, fenofibrate, tamoxifen, and indomethacin have all been studied preclinically (Greene-Schloesser et al. 2014; Jenrow et al. 2010; Liu et al. 2010) but translational trials in this realm have been sparse.

Pioglitazone is a member of the thiazolidinedione class of insulin-sensitizing drugs that has been used in the treatment of type II diabetes mellitus and also acts as a PPAR-γ agonist. There are emerging data that PPAR-γ agonist can be neuroprotective in stroke, Alzheimer's Disease and Parkinson's Disease (Breidert et al. 2002; Chang et al. 2015; Dehmer et al. 2004; Sundararajan et al. 2005; Zhao et al. 2005). Our institution was the first to show that pioglitazone reduces RICD in a rodent model (Zhao et al. 2007). In this study, rats who were fed pioglitazone daily during RT and after performed better on an object recognition task of short-term memory than irradiated rats who did not receive pioglitazone. The hypothesized mechanism of neuroprotection is via a transcriptional inhibition effect on the NF-κB pathway which is a key mediator of the pro-inflammatory cascade triggered by RT. Chronic oxidative stress and inflammation are postulated to be the cause of normal tissue injury after RT leading to cognitive decline (Greene-Schloesser et al. 2012; Robbins and Zhao 2004). Studies also suggest that PPAR-γ agonists, including drugs in the thiazolidinedione class, can inhibit the growth of cell lines for prostate, ovarian, non-small cell lung, pancreatic, glioma and colon cancers (Grommes et al. 2004; Ban et al. 2010, 2011; Choudhary et al. 2010; Dong et al. 2009; Kim et al. 2011; Yokoyama et al. 2011). These data are encouraging, and there is great interest in doing a clinical trial in humans to see if the protective effect of pioglitazone seen in rodents is also seen in irradiated brain tumor patients.

Pioglitazone was FDA approved for the treatment of type II diabetes in 2012, and its toxicity profile is well documented. The most common toxicities of pioglitazone include peripheral edema, headache, dizziness, arthralgia, back pain, and infections. Hypoglycemia is also a reported toxicity but found more commonly when used in combination with another anti-hyperglycemic medication. The most serious toxicity is the increased risk of heart failure. A JAMA meta-analysis showed a 2.3% rate of serious heart failure in patients taking pioglitazone for diabetes (Lincoff et al. 2007). The rate was much lower in patients taking it for 6 months or less (only 4 patients out of more than 1,000 taking pioglitazone for 6 months or less developed heart failure). There have been reports of an increased incidence in bladder cancer for patients on pioglitazone, but the data are conflicting and inconclusive. Several recently published meta-analyses found either no definitive association between pioglitazone exposure and the development of bladder cancer or a very small association (Filipova et al. 2017; Li et al. 2017; Tang et al. 2018).

The population of brain tumor patients is unique when compared to any of the other populations in which the safety and efficacy of pioglitazone have been evaluated in the past. First, most brain tumor patients are often normoglycemic and using pioglitazone could potentially lead to hypoglycemia. Second, brain tumor patients often receive steroids which can cause hyperglycemia, weight gain, and extremity edema. While pioglitazone may beneficially counteract steroid-induced hyperglycemia, weight gain and edema are side effects of both steroids and pioglitazone. Concurrent use of steroids and pioglitazone might synergistically lead to unacceptable weight gain and edema. Additionally, brain tumor patients are often taking antiepileptic medications and chemotherapy. The interaction of pioglitazone with these agents is not well understood. As a result, before designing

a trial to determine the efficacy of pioglitazone as a cytoprotective agent to mitigate RICD, we needed to evaluate its safety in a population of brain tumor patients.

Materials and methods

Eligibility and exclusion criteria

Given that the safety of pioglitazone was not anticipated to differ by brain tumor tissue type, this study enrolled patients with primary or metastatic brain tumors. Patients > 18 years old who were anticipated to receive at least 10 treatments of RT (at 3 Gy per fraction or less) were eligible. Patients with a history of diabetes, NYHA class III or IV heart failure or symptomatic peripheral edema (grade 2 or greater) were not eligible for enrollment. Patients taking insulin or oral hypoglycemic agents for steroid-induced hyperglycemia were ineligible as were patients with a history of an allergic reaction to any thiazolidinedione. Patients could not be pregnant. Patients could not be taking any medication with a known interaction with pioglitazone or medications know to be a CYP34A inhibitor. Patients with a non-fasting blood glucose > 200 mg/dl, a fasting blood glucose > 125 mg/dl, AST or ALT > 2.5 the upper limit of normal, serum creatinine > 1.5, or hematocrit < 33% (men) or 30% (women) were not eligible for enrollment. Patients with uncontrolled intercurrent illness or unable to provide informed consent were also ineligible.

Trial design and drug therapy

This was phase I, single-institution, open-label, 3 + 3 dose-escalation trial with two dose levels (22.5 mg and 45 mg) and a planned dose-expansion phase. For each patient, their pioglitazone dose was assigned at enrollment and remained fixed. Pioglitazone was taken 5 days per week (Monday through Friday) during radiation and for 6 months after radiation. Patients were evaluated for adverse events including weight gain, edema, heart failure, or lab abnormalities attributable to pioglitazone weekly during RT and then at 1 month, 3 months and 6 months after the completion of RT. Patients were asked to keep a drug diary to monitor compliance. A dose-limiting toxicity (or DLT) was defined as (1) CTC 3.0 grade 3 weight gain, (2) grade 3 edema on the Peripheral Extremity Edema Scale, (3) CTC 3.0 grade 3 hypoglycemia and (4) New York Heart Association (NYHA) Classification of Heart Failure Grade 3 symptoms of heart failure. We selected these specific toxicities as DLTs since the safety of pioglitazone has been extensively evaluated in the past and our concern was potential magnification of weight gain, edema, hypoglycemia and heart failure in a brain tumor population. To estimate the toxicity rate within ± 26% with 95% confidence, we anticipated needing 14 patients enrolled at the same dose level. We planned to enroll 18 patients to account for dropout. Pre-defined stopping rules specified that the study would be stopped if two patients experienced a DLT at the first dose level or if four patients total experienced a DLT. This study was approved by the Wake Forest Baptist Institutional Review Board (CCCWFU 97409). An IND exemption was procured from the FDA (IND 109658). Pioglitazone was purchased from Takeda Pharmaceuticals USA, Inc.

Results

18 patients were enrolled between August 2010 and 2014. 10 patients (55.6%) were female and 17 (94.4%) were white with a median age of 54 years (Table 1). The majority of patients ($n = 14$) received whole brain irradiation for brain metastases. Four patients received partial brain irradiation for primary brain tumors and all four of these patients received concurrent chemotherapy with either temozolomide or bevacizumab or a combination of the two. Three of these patients had recurrent gliomas and were receiving re-irradiation. Three of these four patients also received chemotherapy after radiation (one had a rapid decline in performance status after radiation and was admitted to hospice). Most patients ($n = 13$) had a BMI categorizing them as overweight or obese and most

Table 1 Patient characteristics

Age at registration [median (min, max)]	54 (31, 83)
Gender	
Female	10 (55.6%)
Male	8 (44.4%)
Race	
White	17 (94.4%)
Black	1 (5.6%)
BMI [median, (min, max)]	26.7 (18.7, 34.8)
Tumor type	
Primary	4
Metastatic	14
Radiation dose in Gy [median, (min, max)]	30 (30, 59.4)
Re-irradiation	
Yes	3
No	15
Concurrent chemotherapy during RT	
Yes	4
No	14
Taking steroids at any point during pioglitazone treatment	
Yes	16
No	2

Table 2 Adverse events attributable to pioglitozone in the nine patients in the dose-escalation phase

Event, according to body system and grade	Number of patients	
	Level 1—22.5 mg ($n=3$)	Level 2—45 mg ($n=6$)
Dizziness, grade 3	–	1
Edema: limb, grade 1	1	2
Edema: limb, grade 2	–	1
Fatigue (asthenia, lethargy, malaise), grade 2	–	1
Fatigue (asthenia, lethargy, malaise), grade 4	1	–
Gastrointestinal—other (excessive thirst), grade 2	1	–
Glucose, serum-high (hyperglycemia), grade 2	1	2
Hair loss/alopecia (scalp or body), grade 1	–	2
Hyperpigmentation, grade 1	1	–
Infection—other (shingles), grade 2	1	–
Lymphopenia (1–5.1), grade 2	–	1
Mucositis/stomatitis (functional/symptomatic): oral cavity, grade 1	1	–
Neurology—other (lack of concentration), grade 1	1	–
Neuropathy: motor, grade 3	1	–
Pain: back, grade 1	1	–
Pain: bone, grade 2	1	–
Pain: muscle, grade 1	1	–
Rash: dermatitis associated with radiation; radiation, grade 1	1	–
Vomiting, grade 1	–	1

Attribution of "possible," probable", or "related"

Table 3 Adverse events attributable to pioglitozone in the nine patients in the dose-expansion phase

Event, according to body system and grade	Number of patients (percent)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Edema: head and neck	1 (11)	–	–	–	–
Edema: limb	2 (22)	–	–	–	–
Fatigue (asthenia, lethargy, malaise)	–	–	1 (11)	–	–
Glucose, serum-high (hyperglycemia)	1 (11)	–	–	–	–
Seizure	–	1 (11)	–	–	–

Attribution of "possible," probable", or "related"

($n=16$) took steroids at some point during their treatment course.

No pre-specified DLTs were identified. In the dose-escalation phase, three patients received 22.5 mg and six patients received 45 mg. The adverse events according to dose level in the dose-escalation phase are reported in Table 2. There were only three instances of grade ≥ 3 toxicity: one instance of neuropathy in a patient receiving 22.5 mg, one instance of fatigue in a patient receiving 22.5 mg and one instance of dizziness in a patient receiving 45 mg. The attribution in each of these cases was considered "possible". In the dose-expansion phase, nine patients received 45 mg and there was only one grade 3 toxicity (fatigue) which was also considered possibly attributable to pioglitazone (Table 3).

Table 4 Treatment and outcomes

Pioglitazone dose	
22.5 mg	3 (16.7%)
45 mg	15 (83.3%)
Duration of treatment from registration to last dose (months) [median, (min, max)]	1.4 (0.3, 8.6)
Duration of follow-up (months) [median, (min, max)]	3.1 (0.5, 15.2)
Median survival (months) (95% CI)	5.5 (1.7, 13.2)
Number of deaths	12

The average time that patients remained on pioglitazone treatment was 1.4 months. All but one patient discontinued pioglitazone because of a decline in their performance status related to disease progression. One patient electively

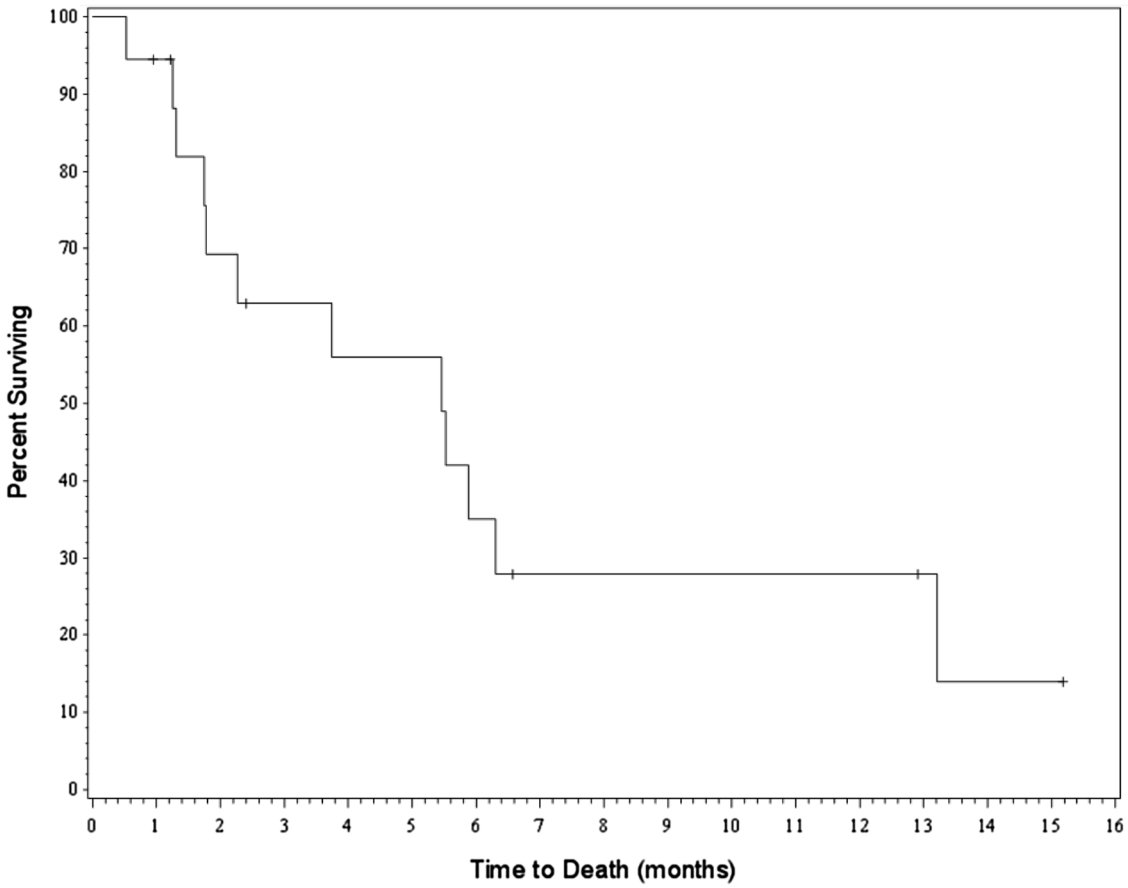

Fig. 1 Patient survival

discontinued pioglitazone after developing grade I lower extremity edema. Median survival was 5.5 months (Table 4; Fig. 1) and median follow-up time was 3.1 months.

Discussion

Pioglitazone at 22.5 mg and 45 mg is well tolerated by brain tumor patients undergoing RT. There were no pre-specified DLTs observed. Specifically, there were no instances of heart failure, hypoglycemia, extreme weight gain, or excessive peripheral edema which are recognized dose-limiting toxicities of this agent. Fatigue, dizziness, and neuropathy were observed. Pioglitazone appears to be safe in a population of brain tumor patients despite a pre-study concern for the potential of overlapping toxicities with steroids.

Several approaches to treating or preventing RICD are presently being explored in clinical trials including cytoprotective medications (Attia et al. 2014), symptom-relieving drugs (Brown et al. 2013; Rapp et al. 2015), and avoidance of critical targets within the brain that mediate cognitive performance post-radiotherapy (Gondi et al. 2014; Peiffer et al. 2013). Presently, a single-arm prospective study has been opened by the Wake Forest NCORP to assess the efficacy of ramipril in preventing RICD in glioblastoma patients. The concern for ramipril is the ability to penetrate the blood–brain barrier sufficiently at clinically tolerable doses. Pioglitazone has been shown to penetrate the blood–brain barrier, and, therefore, represents an intriguing cytoprotective option (Grommes et al. 2013). Moreover, pioglitazone exerts anti-neoplastic effects on glioma cell lines (Grommes et al. 2004) and preclinical models (Ching et al. 2015; Papi et al. 2009).

The efficacy of pioglitazone in mitigating RICD in the preclinical setting has been shown in a rodent study published by Zhao et al. (2007). In this study, adult F344 rats were randomized to pioglitazone vs. no pioglitazone before, during and after whole brain irradiation for a total of 54 weeks of administration. Cognitive function, as measured by the novel object recognition test, was preserved in rats receiving pioglitazone during their whole brain irradiation. Fenofibrate, PPARα agonist, has also been shown in preclinical studies to protect rats from RICD (Greene-Schloesser et al. 2014). In another mouse study, fenofibrate prevented a radiation-induced decrease in the number of newborn hippocampal neurons 2 months after whole brain irradiation

(Ramanan et al. 2009). Moreover, the effects of fenofibrate were abolished in knockout mice, confirming the PPAR-mediated mechanism of preventing brain injury.

This study has several limitations. First, this was a heterogeneous sample that included primarily patients with brain metastases but also four glioma patients who received concurrent and adjuvant chemotherapies. Three of those four glioma patients were receiving their second course of radiation. This cohort was selected because the safety profile of pioglitazone was not anticipated to be different for primary or secondary gliomas; however, differences in radiation therapy dose and regimen are a limitation. Second, patient survival and follow-up were short which precluded any evaluation of chronic, late side effects from pioglitazone. The short survival is unsurprising since most enrolled patients had brain metastases for which they received whole brain RT. These limitations notwithstanding, this is the first trial to evaluate the safety of pioglitazone in brain tumor patients. There is preclinical evidence that pioglitazone may be able to mitigate RICD. Now that the short-term safety of pioglitazone has been established in the brain tumor population, we can move forward with evaluations of the efficacy of pioglitazone for this purpose. Presently, a phase II study is being planned with the goal of determining efficacy in mitigating RICD compared to a historical glioblastoma population and assessing the sample size necessary to power a potential randomized phase III trial.

Conclusion

Pioglitazone was well tolerated by brain tumor patients undergoing RT and no DLT was identified. 45 mg appears to be a safe dose to use in future efficacy trials.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Data availability The clinical data used to support the findings of this study are included within the article. The clinicaltrials.gov number associated with this protocol is NCT01151670.

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