ORIGINAL RESEARCH

Concurrent whole brain radiotherapy and short-course chloroquine in patients with brain metastases: a pilot trial

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Abstract

Objective The immune modulatory drug chloroquine (CQ) has been demonstrated to enhance survival following radiotherapy in patients with high-grade glioma in a clinical trial, but the efficacy in patients with brain metastases is unknown. We hypothesized that short-course CQ during whole brain radiotherapy (WBRT) would improve response to local therapy in patients with brain metastases.

Methods A prospective, single-cohort study was performed combining WBRT with concurrent CQ to assess both the feasibility of and intracranial response to combined therapy in patients with brain metastases. Safety, tolerability, and overall survival of this combination were also examined, along with allelic status of *IDO2* (indoleamine 2,3-dioxygenase 2), an immune modulatory enzyme inhibited by chloroquine that may affect survival outcomes. CQ therapy (250 mg by mouth daily) was initiated 1 week before WBRT (37.5 in 2.5 Gy daily fractions) in patients with newly diagnosed brain metastases from biopsy-proven, primary lung, breast, or ovarian solid tumors ($n=20$). The primary endpoint was radiologic response 3 months after combined CQ and WBRT therapy. Secondary endpoints included toxicity and overall survival. Patients were stratified by *IDO2* allelic status.

Results After a median clinical follow-up of 5 months (range, 0.5–31), 16 patients were evaluable for radiologic response which was complete response in two patients, partial response in 13 patients, and stable disease in one patient. There were no treatment-related grade≥3 toxicities or treatment interruption due to toxicity. Median and mean overall survival was 5.7 and 8.9 months, respectively (range, 0.8–31). A trend toward increased overall survival was observed in patients with wild-type *IDO2* compared to patients with heterozygous or homozygous configurations that ablate *IDO2* enzyme activity (10.4 vs. 4.1 months; $p=0.07$).

Conclusions WBRT with concurrent, short-course CQ is well-tolerated in patients with brain metastases. The high intracranial disease control rate warrants additional study.

Keywords Brain metastases · Chloroquine · Immunotherapy · Immunomodulation · Indoleamine 2,3-dioxygenase (Ido) · Non-small cell lung cancer (Nsclc) · Whole brain radiotherapy

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Introduction

Brain metastases are a major cause of morbidity and mortality in patients with cancer, affecting up to 200,000 patients a year in the US alone [1]. The majority of brain metastases originate from common cancer-like lung (40–50 %), breast (15–25 %), and melanoma (10 %). These lesions may occur synchronously with other sites of systemic metastasis(es), but they occur frequently as the only site of disease in patients with excellent performance status and systemic disease control [2–4]. While patients with a single or limited number of brain metastases may benefit from neurosurgical resection or stereotactic radiosurgery (SRS), many patients present with multiple, diffuse intracranial metastases that are not amenable to such therapies

due to tumor location, number of lesions, or comorbid conditions.[2–4] Thus, a viable option for the treatment of many brain metastases patents, even those with poor performance status, is whole brain radiotherapy (WBRT) which represents a standard of care [5]. Given the prevalence of this condition and its dismal prognosis, the treatment of brain metastases should continue to evolve.

Regardless of treatment, the survival times of patients with brain metastases remain extremely poor with a median survival of 3.4 months. The 6-month, 1-, and 2-year survival rates for these patents are 36, 12, and 4 %, respectively [6, 7]. The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) and the later updated Graded Prognostic Assessment (GPA) have identified prognostic factors of patients with brain metastases to stratify the heterogenous population into prognostic classes. Using these criteria, patients with the most favorable prognostic factors still only have a predicted median survival of 11 months [8–10]. Ultimately, 30–50 % of patients with brain metastases will die of their central nervous system disease [5, 6, 8], reinforcing the urgent need for improved therapies to treat this condition.

One way to potentially enhance standard WBRT would be to use radiation sensitizers. Chloroquine (CQ) is a potential radiation sensitizer that has been employed for decades as an antimalarial agent. Its clinical use has a well-established safety profile. CQ and its derivatives have gained interest in recent years due to their ability to modulate inflammation, immune response, and sensitivity to cancer therapy. Most CQ-related studies have focused on its ability to block autophagy, a cellular process that sustains cancer cell survival under therapeutic stress. CQ has also been found to activate the p53 pathway and induce apoptosis in glioma cells [11]. Of particular interest, a prospective, randomized, clinical trial evaluating low-dose CQ in the treatment of high-grade gliomas reported enhanced treatment response and improved overall survival (OS) with the addition of CQ to external beam radiotherapy and chemotherapy[12, 13]. To date, CQ therapy has not been evaluated in patients receiving radiotherapy for treatment of brain metastases.

IDO2 is a tryptophan catabolic enzyme implicated in suppressing T cell immunity in the tumor microenvironment where its pharmacologic inhibition may potentiate cancer chemotherapy [14–16]. IDO2 is a relative of the better-known enzyme IDO that is widely implicated in cancer progression through an ability to block T cell-mediated immune surveillance by supporting the expansion of T regulatory cells and myeloid-derived suppressor cells [16–18]. While less widely expressed than IDO, it is evident that IDO2 is expressed in brain [15]. Remarkably, there is a wide variation in IDO2 function in human populations based on the broad distribution of two single-nucleotide polymorphisms (SNPs) in the coding region of the human IDO2 gene that reduce or abolish its enzyme activity [15]. The broad distribution of these genetic variations may therefore vary an individual's ability to respond to drugs that target IDO2 since not all individuals express a fully active enzyme. CQ has been found to be a potent and selective inhibitor of IDO2 (R.M., unpublished observations), prompting the notion that CQ might enhanced the efficacy of WBRT in a manner associated with IDO2 genotype.

Based on the improved clinical outcomes reported with concurrent use of CQ and partial brain radiotherapy in some patients with high-grade glioma [12, 13], we hypothesized that CQ might potentiate the therapeutic effect of WBRT for brain metastases. In this study, patients are stratified by IDO2 genotype in the event that IDO2-inactivating SNPs blunt clinical responses to CQ therapy.

Methods

Patient selection After Institutional Review Board approval of the protocol, all patients provided informed consent. Adult patients with a histologically confirmed primary solid malignancy and evidence of single or multiple brain metastases on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans were eligible for this prospective study. Metastatic lesions were required to be less than 5 cm in diameter, and radiographic findings could not be consistent with leptomeningeal metastases. Patients were only eligible to receive CQ after clearance from their physician that the drug should not pose a medical problem to the patient. Patients were excluded from the study if they had received prior radiotherapy to the brain, were pregnant or nursing, or had a history of hypotension, cardiomyopathy, epilepsy or seizure disorder, impaired renal function, psoriasis, porphyria, or known hypersensitivity to 4-aminoquinoline compounds. Patients were also excluded if, during the CQ treatment, they complained of any visual or auditory disturbances or suffered from severe acute gastrointestinal problems like vomiting, diarrhea, or abdominal cramps.

Radiotherapy WBRT was delivered with 6 to 10 MV photons to a total dose of 37.5 Gy in 2.5 Gy once daily fractions over a course of 3 weeks. Each patient was treated in the supine position while wearing a head immobilization mask to ensure that daily positioning was reproducible. Target volumes included the entire cranial contents, with flashing beyond skin and a minimum margin of 0.75 cm on the skull-base as visualized on the simulator or portal films to account for beam penumbra and day-to-day set-up variation. The ocular lens was shielded from the direct beam at all times using collimators. SRS boost after WBRT has been validated by randomized trials to improve local control in patients with 1–4 brain metastases and to improve survival in patients with a single brain metastasis [19, 20]. Patients were permitted to receive

SRS boost if posttreatment imaging revealed residual disease or if this therapy was recommended at the discretion of the treating physician (AD).

Chloroquine therapy Chloroquine branded as Aralen (Sanofi-Aventis U.S., Bridgewater, NJ) was used in this study. CQ therapy began 1 week prior to initiation of WBRT and was administered daily (250 mg/day) for a total of 5 weeks.

IDO2 genotyping One week prior to WBRT, 5 mL of blood was collected from each patient and stored for subsequent *IDO2* genotyping. Standard methods were used to isolate genomic DNA from blood cells, perform PCR, and define the DNA sequence of the *IDO2* SNPs as described [15]. The coding region SNP in exon 8 is rs10109853 (C/T encoding R248W change) which attenuates the IDO2 enzyme activity ~90 % in vitro [15]. The coding region SNP in exon 10 is rs4503083 (T/A encoding Y359Stop change) which truncates the IDO2 enzyme, completely abolishing its catalytic activity [15].

Patient monitoring Baseline clinical assessments were performed for each patient prior to the start of WBRT and CQ combination therapy. Assessments included medical history, complete physical exam including neurologic examination and mental status exam, complete blood count, and contrast-enhanced imaging of the brain. Most patients received contrast-enhanced MRI imaging of the brain, the preferred imaging method; however, contrast-enhanced CT scans were permitted for evaluation of metastatic disease in patients who could not tolerate MRI or in whom MRI was contraindicated. Patients were assessed for toxicity and clinical response by the radiation oncologist (A.D.) at weeks 1–3 of WBRT and at the 1- and 3-month follow-up and then every 3 months thereafter until death. Brain imaging was also performed at 1- and 3-month follow-up and then every 3 months thereafter until death. Overall survival was calculated from the time of randomization into the study until death or April 1, 2013, whichever occurred first. Patients who were still alive were considered censored.

Endpoints and statistical analysis The primary endpoint was intracranial radiologic response to treatment as determined by brain metastases profile on contrast-enhance CT and MRI scans.

Intracranial tumor response to treatment was not assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), which requires measurable target lesions to have a minimum diameter of 10 mm [21]. RECIST criteria was inappropriate for the patient population recruited for this study, as many patients with BM have multiple, clinically significant lesions that measure less than 10 mm in diameter. Therefore, target lesions acceptable for inclusion in this study had a diameter of ≥4 mm. Partial response (PR) to therapy was defined as 20 % or greater decrease in the sum of the diameters

of target lesions, taking as reference the baseline sum diameters. Complete response (CR) was defined as complete resolution or disappearance of target lesions. Stable disease (SD) occurred when the size of persistent lesions remained unchanged, while progressive disease (PD) occurred when there was unequivocal progression of existing lesions or appearance of new lesions.

Secondary endpoints included toxicity scored according to the National Cancer Institute Common Toxic Criteria for Adverse Events (CTCAE), cause of death, overall survival, interval to intracranial progression, and to correlate survival times with *IDO2* genotypes. Overall survival and interval to intracranial progression were determined using the Kaplan–Meier method. Intention-to-treat analysis was performed to assess patient survival.

Results

Patient evaluation Twenty patients were enrolled in the study between January 2009 and November 2011. The 20 evaluable patients consisted of 11 women and 9 men with a median age of 64 years (range, 47–81). The patient and tumor characteristics are summarized in Table 1. The median duration of WBRT treatment was 20 days (range, 19–23). The median clinical follow-up of all patients was 5 (range, 0.5–31)months from the start of CQ treatment.

Nineteen patients completed WBRT. One patient withdrew after receiving 27.5 Gy of the 37.5 Gy prescribed due to intrathoracic disease progression of non-small cell lung cancer (NSCLC) and clinical deterioration. This patient did not experience a treatment-related adverse event. The remaining 19 patients did complete radiotherapy, and no patient suffered treatment interruption due to adverse effect or toxicity. Two patients received a stereotactic radiosurgery boost to a single intracranial lesion following WBRT. No patient had neurosurgical resection of a metastasis prior to enrollment, and no patient received cytotoxic chemotherapy during the course of WBRT. Four patients did not receive any posttreatment brain imaging due to clinical demise or death and were not included in radiologic response analysis.

Radiographic response and patient survival Contrast-enhanced brain MRI was performed after concurrent CQ and WBRT in 16 patients. The objective intracranial response rate 3 months after WBRT included CR in 2 patients, PR in 13 patients, and stable disease in 1 patient. This response rate corresponded to an objective clinical response of 93 % at 3 months. Intracranial disease control rate was 100, 83, and 55 % at 3, 6, and 12 months, respectively. Among the two patients with CR, one patient had a single lesion while the other had three lesions and neither patient received an SRS

Table 1 Patient and cancer characteristics

Characteristic	Value (%)
Gender	
Male	9 (45)
Female	11 (55)
Age (years)	
Median	64
Range	47–81
Karnofsky Performance Status (KPS)	
90–100	14 (70)
70–80	4 (20)
≤60	2 (10)
Extracranial metastases	
Yes	13 (65)
No	7 (35)
Recursive partitioning analysis (RPA) class [8]	
I	2 (10)
II	16 (80)
III	2 (10)
Graded Prognostic Index (GPI) [9]	
3.5–4	0 (0)
3	3 (15)
1.5–2.5	11 (55)
0–1	6 (30)
Primary tumor type	
Non-small cell lung	17 (85)
Small cell lung	1 (5)
Breast	1 (5)
Ovarian	1 (5)
Number brain metastases	
1	7 (35)
2–4	10 (50)
>5	3 (15)
Median	3
Size brain metastasis (cm)	
Median	0.8
Range	0.4–2.4

boost. Among the 12 patients with a PR to combined therapy, there were 39 brain lesions total with the following responses: 11 lesions CR, 27 lesions PR, and 1 stable lesion. One patient with initial PR was able to achieve a CR following SRS boost. Intracranial progression was confirmed on follow-up imaging in two patients at a median of 7 months following completion of WBRT.

Kaplan–Meier estimates reveal a median overall survival of 5.7 (range, 0.8–31) months. At the time of analysis, two patients were alive, one of whom had a survival time exceeding 30 months. For each patient who died, an attempt was made to determine the cause of death, which was respiratory failure in

two patients, bowel perforation in two patients, pulmonary embolism in one patient, cardiac event in one patient, and due to a second primary malignancy (pancreatic) in one patient. Three patients died in hospice of unspecified causes, and eight patients died of unknown causes.

Treatment toxicity No patient suffered from observed CQ toxicity or radiotherapy treatment interruptions. There were no documented grade 3 or greater toxicities observed during the course of WBRT treatment nor was there any evidence of increased radiation skin reaction or CNS injury due to concurrent administration of CQ as noted in two case studies in the literature [23, 24]. Grade 1 radiation dermatitis was observed in four patients (20 %), and grade 2 alopecia was observed in eight patients (40 %). There were no detectable neurocognitive defects or radiation necrosis. One serious adverse event interpreted as unrelated to study treatment occurred in a patient who developed respiratory failure due to lung cancer progression and pulmonary infection.

IDO2 host genotype and correlation with clinical outcomes Host *IDO2* genotype for the SNPs in coding exons 8 and 10 were determined from blood-derived genomic DNA prepared from patients [15]. Briefly, homozygosity or heterozygosity of enzymatically ablative SNPs at each site were detected in 14/20 patients recruited to the study, where the *IDO2* genotype implied reduced IDO2 activity in this cohort. Conversely, 6/20 patients displayed wild-type alleles at each SNP site, where the *IDO2* genotype implied full IDO2 activity in this cohort. This relative proportion of allelic distributions approximately paralleled that seen in a larger disease-free population that had been characterized previously [15].

Median and mean OS for all patients was 5.7 and 8.9 months (range, 0.8–31 months), respectively, from the time of enrollment. A trend toward improved OS was observed for patients with wild-type *IDO2* ($n=6$) compared to patients with enzymatically ablative SNPs in either exon 8 or 10 ($n=16$) (10.4 vs. 4.1 months; $p=0.07$). Due to the high rates of radiologic response, there was no appreciable difference in response between patients with wild-type *IDO2* compared with enzymatically ablative SNPs. Table 2 summarizes the patient and tumor characteristics associated with SNP patterns. Due to small patient numbers in this pilot trial, some prognostic factors were dissimilar among the two genotype groups.

Discussion

This is the first prospective trial to report a combination of WBRT and concurrent CQ for the treatment of brain metastases. The results demonstrated that this combination was well-tolerated with no observed treatment interruptions due to

Table 2 Patient stratification of prognostic factors to IDO2 genotype

Characteristic	+/+ IDO2 (n=6)	+/p or p/p IDO2 (n=14)
Age (years)		
Median	56	65
Karnofsky Performance Status (KPS)		
Median	90 %	90 %
Extracranial metastases		
Yes	2 (33)	11 (78)
No	4 (66)	3 (12)
Recursive partitioning analysis (RPA) class [8]		
I	2 (33)	0 (0)
II	4 (66)	12 (86)
III	0 (0)	2 (14)
Graded Prognostic Index (GPI) [9]		
3.5–4	0 (0)	0 (0)
3	3 (50)	0 (0)
1.5–2.5	3 (50)	8 (57)
0–1	0 (0)	6 (43)
Number brain metastases		
Median	2	3

+/+, wild-type configuration at exon 8 and exon 10 SNPs in the *IDO2* gene derived from the patient host; +/p or p/p, heterozygosity or homozygosity in either the exon 8 or the exon 10 SNPs in the *IDO2* gene derived from the patient host, both of which ablate the enzymatic activity of the IDO2 enzyme 10-fold or greater [15]

treatment-related toxicity. Two case studies have reported an intensification of skin reactions with bullous eruptions and moist desquamation after concurrent treatment with CQ and external beam radiotherapy [23, 24], but we did not observe these toxicities in our trial. In contrast, the toxicity experienced in this study was in agreement with that reported previously by Sotelo and colleagues from their prospective trial of combined CQ and external beam radiotherapy for glioblastoma multiforme, where they reported no signs or symptoms of retinopathy related to CQ toxicity nor any radiation treatment breaks due to toxicity. These investigators reported an increase in the incidence of seizure during treatment or the clinical follow-up period in glioblastoma patients who received the combined therapy [12, 13]; however, we did not document any similar occurrence in any of the brain metastases patients we treated.

Up to half of patients with brain metastases who receive WBRT will die due to intracranial disease. In our study, intracranial control rates were excellent—100 % at 3 months with 93 % radiologic response. In addition, only two patients developed intracranial progression at a median of 7 months which is clinically meaningful in a patient population with anticipated short survival times.

In addition to the excellent local control provided by combined CQ and WBRT therapy, the data for the secondary endpoints of overall survival and cause of death propose a CQ treatment benefit since neurologic death secondary to brain metastases was not observed. Additionally, the present series demonstrated a median overall survival of 5.7 months which compares slightly favorably to the RTOG recursive partitioning analysis (RPA), which estimates a median survival of 4.2 months for patients in class II [8]. This data also compares favorably with the predicted median survival of 3.8 and 2.6 months for patients with scores of 1.5–2.5 or 0–1, respectively, on the Graded Prognostic Index (GPI)—scores that are representative of most patients in the current series [9]. Larger, randomized studies would be required to confirm the ventured survival benefit from the addition of CQ to standard WBRT, but this data is encouraging. Additionally, it is important to note that a primary goal of WBRT remains the improvement of local tumor control to provide palliation of neurologic problems and prevent progression of symptoms. Thus, improvement in survival may not be the only measure of benefit of a local therapy like WBRT, as overall survival is determined by extracranial disease and comorbid conditions in addition to the presence of brain metastases [34]. Future trials with CQ and WBRT should consider endpoints to measure quality of life, symptom relief, or neurologic progression.

A variety of dose and radiation fractionation schedules have been tested in prospective, randomized trials in patients with multiple brain metastases, but none have improved efficacy or survival, to date [25–28]. Since survival outcomes have not been improved by dose escalation (including doses in excess of 50 Gy), there has been interest in radiation sensitizers to potentiate the efficacy of WBRT. However, a variety of agents have been tested with little, if any, effect on survival. Some trials have even reported serious adverse effects [29–33]. This situation may be changing with more recent promising reports of motexafin gadolinium and efaproxiral as radiosensitizers that can improve quality of life and survival in breast cancer patients with brain metastases [34–36]. Our findings suggest CQ as another agent that might find use in leveraging the efficacy of WBRT to some patients with lung cancer or other cancers where brain metastases frequently occur during progression.

CQ is an antimalarial agent that has been used safely in a variety of clinical settings for decades. CQ exerts complex pleiotropic effects that may enhance radiotherapy, for example, by inhibiting DNA repair or blocking autophagic responses that promote cancer cell survival under stress conditions [37–39]. However, it is also clear that CQ exerts immunomodulatory effects that have been used for years to treat certain autoimmune diseases, such as arthritis and systemic lupus erythematosus, and, more recently, to treat an increasing number of other diseases including cancer [22]. In evaluating the ability of CQ to improve outcomes in brain metastases patients receiving WBRT, our work employed a relatively low dose of CQ not expected to affect DNA repair or autophagy,

based on existing information [39], but consistent with immune modifier effects known to yield beneficial effects in autoimmune disease patients.

In this light, patients were stratified by the patient's genetic status in *IDO2*, an immune modulatory enzyme, to determine if the efficacy of combined CQ and WBRT is rooted mechanistically as immunoradiotherapy. CQ ablates IDO2 enzyme activity and may block T cell-mediated immune surveillance in tumors in those wild-type patients where IDO2 is present as an enzymatically active target. Interestingly, patients with a wild-type configuration of the *IDO2* gene that confers full enzyme activity had an observed median survival that compared favorably with historic controls receiving WBRT alone, including patients with RPA and GPI scores that are representative of the patients in the current series. In this initial study, we cannot rule out the possibility that the dissimilar median survival times of patients with wild-type or enzymatic ablative *IDO2* SNP configuration reflect differences in other prognostic factors that were not balanced fully between the two groups (Table 2). Ultimately, a larger sample size will be required to determine the efficacy of *IDO2* genotype as a biomarker and whether CQ can cause degradation of IDO2-mediated immune escape in patients with a wild-type type configuration of the *IDO2* gene and, in turn, improve T cell-based antitumor immunity.

Conclusion

WBRT with concurrent, short-course CQ is well-tolerated in patients with brain metastases. The high intracranial disease control rate warrants additional study.

Conflict of interest   George C. Prendergast reports a conflict of interest as an inventor and a compensated scientific advisor, grant recipient, and shareholder in New Link Genetics Corporation, which has licensed IDO2 technology patented by the Lankenau Institute for Medical Research. James B. DuHadaway and Richard Metz report related conflicts as inventors and shareholders in New Link Genetics Corporation. Harriett Belding Eldredge, Albert DeNittis, and Michael Chernick declare that they have no conflict of interest.

Ethical statement   Human investigations described in this study were approved by the Main Line Health Institutional Review Board, and all procedures were performed in accordance with its ethical standards and with those of the Helsinki Declaration of 1975 as revised in 2008.

Statement of informed consent   All persons involved in this study gave their informed consent prior to their inclusion in the study, as required by the procedures approved by the Main Line Health Institutional Review Board.

References

1. Gavrilovic IT, Posner JB (2005) Brain metastases: epidemiology and pathophysiology. J Neurooncol 75(1):5–14
2. Delattre JY et al (1988) Distribution of brain metastases. Arch Neurol 45(7):741–744
3. Nussbaum ES et al (1996) Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 78(8):1781–1788
4. Posner JB (1978) Neurologic complications of systemic cancer. Dis Mon 25(2):1–60
5. Videtic GM et al (2009) American College of Radiology appropriateness criteria on multiple brain metastases. Int J Radiat Oncol Biol Phys 75(4):961–965
6. Lagerwaard FJ et al (1999) Identification of prognostic factors in patients with brain metastases: a review of 1,292 patients. Int J Radiat Oncol Biol Phys 43(4):795–803
7. Lutterbach J, Bartelt S, Ostertag C (2002) Long-term survival in patients with brain metastases. J Cancer Res Clin Oncol 128(8):417–425
8. Gaspar L et al (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37(4):745–751
9. Sperduto CM et al (2008) A validation study of a new prognostic index for patients with brain metastases: the Graded Prognostic Assessment. J Neurosurg 109(Suppl):87–89
10. Sperduto PW et al (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 77(3):655–661
11. Kim EL et al (2010) Chloroquine activates the p53 pathway and induces apoptosis in human glioma cells. Neuro Oncol 12(4):389–400
12. Briceno E, Calderon A, Sotelo J (2007) Institutional experience with chloroquine as an adjuvant to the therapy for glioblastoma multiforme. Surg Neurol 67(4):388–391
13. Sotelo J, Briceno E, Lopez-Gonzalez MA (2006) Adding chloroquine to conventional treatment for glioblastoma multiforme: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 144(5):337–343
14. Hou DY et al (2007) Inhibition of indoleamine 2,3-dioxygenase in dendritic cells by stereoisomers of 1-methyl-tryptophan correlates with antitumor responses. Cancer Res 67(2):792–801
15. Metz R et al (2007) Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor IDO inhibitory compound D-1MT. Cancer Res 67:7082–7087
16. Katz JB et al (2008) Indoleamine 2,3-dioxygenase in T-cell tolerance and tumoral immune escape. Immunol Rev 222:206–221
17. Munn DH, Mellor AL (2007) Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest 117(5):1147–1154
18. Smith C et al (2012) IDO Is a nodal pathogenic driver of lung cancer and metastasis development. Cancer Discov 2(8):722–735
19. Andrews DW et al (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363(9422):1665–1672
20. Kondziolka D et al (1999) Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys 45(2):427–434
21. Eisenhauer EA et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2):228–247
22. Ben-Zvi I et al (2012) Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allergy Immunol 42(2):145–153
23. Munshi A et al (2008) Unusual intensification of skin reactions by chloroquine use during breast radiotherapy. Acta Oncol 47(2):318–319
24. Rustogi A, Munshi A, Jalali R (2006) Unexpected skin reaction induced by radiotherapy after chloroquine use. Lancet Oncol 7(7):608–609

25. Borgelt B et al (1981) Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 7(12):1633–1638

26. Davey P et al (2008) A phase III study of accelerated versus conventional hypofractionated whole brain irradiation in patients of good performance status with brain metastases not suitable for surgical excision. Radiother Oncol 88(2):173–176

27. Haie-Meder C et al (1993) Results of a randomized clinical trial comparing two radiation schedules in the palliative treatment of brain metastases. Radiother Oncol 26(2):111–116

28. Murray KJ et al (1997) A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. Int J Radiat Oncol Biol Phys 39(3):571–574

29. Antonadou D et al (2002) Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. J Clin Oncol 20(17):3644–3650

30. DeAngelis LM et al (1989) The combined use of radiation therapy and lonidamine in the treatment of brain metastases. J Neurooncol 7(3):241–247

31. Eyre HJ et al (1984) Randomized trial of radiotherapy versus radiotherapy plus metronidazole for the treatment metastatic cancer to brain. A Southwest Oncology Group study J Neurooncol 2(4):325–330

32. Komarnicky LT et al (1991) A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). Int J Radiat Oncol Biol Phys 20(1):53–58

33. Phillips TL et al (1995) Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89–05. Int J Radiat Oncol Biol Phys 33(2):339–348

34. Mehta MP et al (2009) Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients with brain metastases: results of a phase III trial. Int J Radiat Oncol Biol Phys 73(4):1069–1076

35. Scott C et al (2007) Improved survival, quality of life, and quality-adjusted survival in breast cancer patients treated with efaproxiral (Efaproxyn) plus whole-brain radiation therapy for brain metastases. Am J Clin Oncol 30(6):580–587

36. Suh JH et al (2006) Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. J Clin Oncol 24(1):106–114

37. Jensen PB, Sehested M (1997) DNA topoisomerase II rescue by catalytic inhibitors: a new strategy to improve the antitumor selectivity of etoposide. Biochem Pharmacol 54(7):755–759

38. Sorensen M, Sehested M, Jensen PB (1997) pH-dependent regulation of camptothecin-induced cytotoxicity and cleavable complex formation by the antimalarial agent chloroquine. Biochem Pharmacol 54(3):373–380

39. Amaravadi RK et al (2011) Principles and current strategies for targeting autophagy for cancer treatment. Clin Cancer Res 17(4):654–666