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FET-PET-based reirradiation and chloroquine in patients with recurrent glioblastoma

First tolerability and feasibility results

Introduction

Despite increasing insights into its biology, glioblastoma multiforme (GBM) remains a devastating disease and a therapeutic challenge. For patients with recurrent GBM (rGBM), there are no established therapies. Patients may be treated with reoperation, reirradiation (re-RT), and different systemic regimes, but median survival is only between 6 and 10 months independent of the therapeutic approach [3, 10]. Re-RT treatment planning using molecular imaging with amino acid tracers, such as ^{18}fluoro-*O*-(2) fluoroethyl-l-tyrosine ([^{18}F]FET) and [^{11}C]methionine (MET), may improve the efficacy of re-RT [5] by better coverage of the planning target volume (PTV) and sparing of normal tissue. However, this approach does not solve the problem of the high radioresistance of GBM [13].

One of the mechanisms that can contribute to decreased sensitivity toward ionizing radiation (IR) is autophagy [14]. This phenomenon represents a catabolic process in which toxic and damaged cellular components are degraded via the lysosomatic pathway and used for the generation of new amino acids, fatty acids, sugars, and nucleosides. After recycling, these compounds are used for new macromolecular synthesis and energy production [11]. In neoplastic disease, autophagy may either stimulate or inhibit carcinogenesis depending on tumor type, stage, and genetic background [20]. In glioma cells, autophagy can strongly promote cellular survival [6, 9].

In our previous work, we demonstrated that treatment with chloroquine (CQ), an antimalarial and immunomodulatory drug, strongly promoted γIR-induced cell death in highly radioresistant stem-like glioma cells [2]. It has been reported that in irradiated A172 glioma cells, CQ augmented apoptotic cell death [8]. Moreover, CQ suppressed tumor growth in an orthotopic glioma (U87MG) mouse model via activation of the p53 pathway [7]. In one randomized, double-blind, placebo-controlled trial in patients with newly diagnosed GBM, CQ was added to conventional RT and chemotherapy with lomustine (CCNU). Combined treatment was well tolerated and no significant CQ related toxicity was observed. Median survival after surgery was 24 months for CQ-treated patients compared with 11 months for controls [17].

On the basis of these data, we treated a small series of patients with re-RT and CQ and observed encouraging responses, which we would like to present in this report.

Case reports

Between January 2012 and August 2013, we treated five patients with histologically proven rGBM. Stereotactic fractionated re-RT was performed with the BrainLAB system (BrainLAB, Heimstetten, Germany). Precise patient immobilization was achieved with a bite-plate mask system. Planning for all patients was carried out using amino acid positron emission tomography (PET)/computed tomography (CT) and magnetic resonance imaging (MRI) image fusion. In four patients, the gross tumor volume (GTV) was defined as the contrast-enhancing area on CT/T1 gadolinium (Gd)-enhanced MRI image fusion (without surrounding edema) and the complete region of increased amino acid tracer uptake on amino acid PET/CT. To define the planning target volume (PTV), the GTV was expanded by 3 mm in all directions. In one patient, who after surgery for rGBM did not have visible or viable tumor on MRI or FET-PET/CT, clinical tumor volume (CTV) was defined as the visible resection cavity, and for definition of planning target volume (PTV), a 4-mm margin was added in all directions. In all these cases, the anatomical/biological image fusion was performed as previously described [13]. The dose was prescribed to the 95 % isodose line, which covered the PTV. Treatment was performed with a total dose between 35 and 50 Gy, given as 2–5 Gy daily con-

Angelika Bilger and Martin-Immanuel Bittner contributed equally to this work.

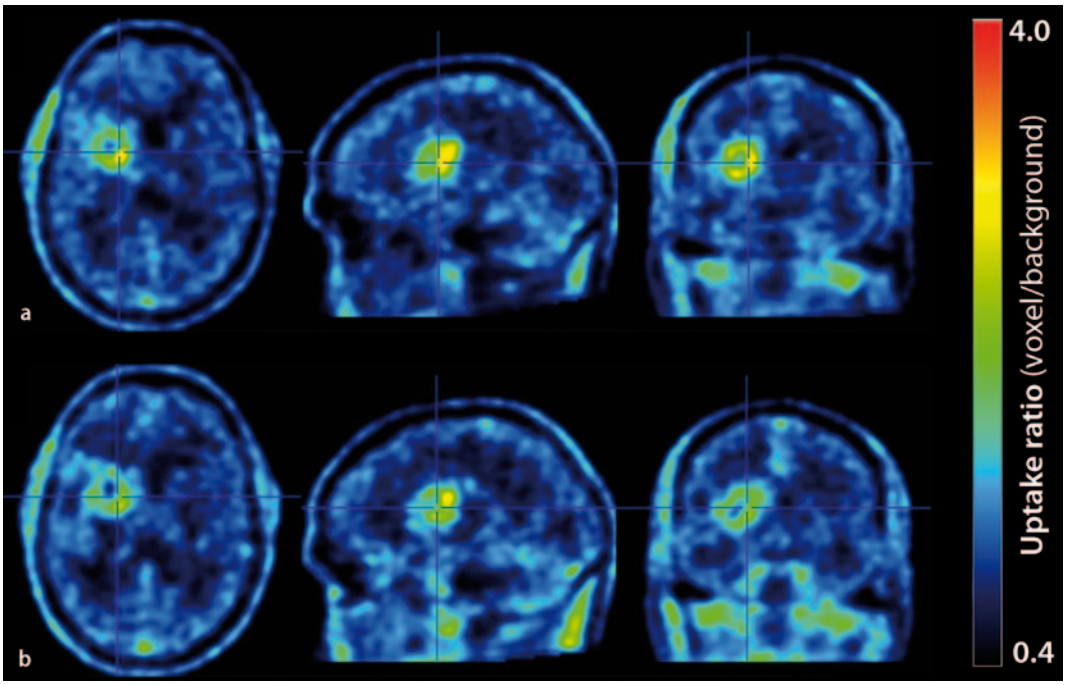

Fig. 1 ◀ ^{18}Fluoro-*O*-(2) fluoroethyl-l-tyrosine positron emission tomography (FET-PET) shows FET uptake before (**a**) and after reirradiation and chloroquine administration (**b**) in patient 3 with primary inoperable GBM who displayed progressive disease under treatment with temozolomide. Two months after therapy, a reduction of tumor volume by 25 % was observed. Tumor volume was defined as tissue exceeding a tissue/background ratio of 2.0 (LIT)

tinually over 5 days, excluding Saturday and Sunday. Three days before initiating re-RT, the first dose of 250 mg of CQ was administered. One patient received additionally four cycles of CCNU chemotherapy (80 mg/m^2)—on the first day of re-RT and every 6 weeks thereafter. All patients provided written informed consent. The study was approved by the ethics committee of the Albert Ludwig University of Freiburg and was performed according to the Declaration of Helsinki.

Patient 1

In May 2006, a 38-year-old male patient was diagnosed with oligoastrocytoma (WHO grade II). He was treated with four cycles of procarbazine/CCNU chemotherapy. In July 2009, MRI revealed progress in the right parietal lobe. Pathologic examination of the biopsy specimen confirmed diagnosis of GBM WHO grade IV. The tumor was resected and the patient was treated with combined radiochemotherapy (RCHT) according to the EORTC 26981/22981-NCIC CE3 protocol [18] between August and October 2009. From November 2009 to May 2010, seven cycles of TMZ (5/23-day protocol) were administered. In June 2010, MRI showed tumor progression in the right parietal lobe. In July 2010 he was reoperated and between August and December 2011, he was treated adjuvantly with eight TMZ cycles (5/23-day protocol). In December 2011, follow-up MRI and FET-PET/CT were performed and detected progression in the resection area and a new lesion in the left temporal region. During January and February 2012, the resection area was reirradiated with a total dose of 39 Gy (5×3 Gy/week) and the new lesion with a total dose of 35 Gy (7×5 Gy/week). Three days before commencing re-RT, the first dose of 250 mg CQ was administered. Subsequently, the patient took CQ daily during and after re-RT. In April 2012, FET-PET/CT revealed partial response of both treated lesions and he continued to take 250 mg CQ daily. In November 2012, MRI showed progressive disease (PD) and the patient was treated with TMZ (7/7-day protocol, 16 cycles) together with 250 mg CQ. In May 2013, MRI revealed PD and in June that year he refused to have any tumor-specific therapy. At the time of writing, he is still alive (ECOG 4).

Patient 2

In July 2010, a 56-year-old male patient was diagnosed with GBM (WHO grade IV) in the right frontal lobe. The tumor was resected and between August and September 2010, he was treated according to the EORTC 26981/22981-NCIC CE3 protocol [14]. From November 2010 to February 2011, five cycles of TMZ were administered (treatment was discontinued at the patient's request). In January 2012, MRI showed PD in the right frontal and the periventricular region and he was reoperated in February 2012. Postoperative MRI and FET-PET/CT in February 2012 revealed a viable residual tumor. The tumor was treated with re-RT from March to April 2012 (5×3 Gy/week, total dose 39 Gy). The first 250 mg CQ dose was administered 3 days before starting re-RT and the patient took CQ daily during and after re-RT. MRI showed stable disease in May 2012 and he continued to take 250 mg CQ daily. MRI in September 2012 revealed PD. Between October 2012 and February 2013 he was treated with ten cycles of bevacizumab + CCNU + 250 mg CQ. In March 2013, PD was observed on MRI. The patient refused further tumor-specific therapy and died in May 2013.

Patient 3

In March 2011, MRI showed contrast enhancement in the right basal ganglia of a 56-year-old patient. Pathologic examination revealed GBM (WHO grade IV). Due to the tumor location, neurosurgeons hesitated to perform sur-

gery and the patient received a combined RCHT according to the EORTC 26981/22981-NCIC CE3 protocol [14] from March to May 2011. In the following 2 months, he received two cycles of TMZ (5/23-day protocol). From August 2011 to April 2012, the patient was treated with another 18 cycles of TMZ (7/7-day protocol). In April 2012, FET-PET and MRI detected PD. In the same month he presented to our clinic in good clinical condition (ECOG 1) reporting only mild sensitivity deficiency of the left hand. In April and May 2012, we treated him with re-RT (5×3 Gy/week, total dose 39 Gy). The first 250 mg CQ dose was administered 3 days before starting re-RT and the patient took CQ daily during and after re-RT. In July 2012, FET-PET/CT detected decreased tracer uptake in the treated area (**Fig. 1**). He continued to take 250 mg CQ daily together with TMZ (4 cycles, 7/7-day protocol) and died in October 2012 due to pulmonary embolism.

Patient 4

In July 2011, a 62-year-old male patient was diagnosed with GBM (WHO IV) of the right temporal lobe. In the same month, the tumor was surgically resected and the patient was treated adjuvantly with bevacizumab and irinotecan (multicenter GLARIUS trial). In March 2013, MRI detected PD on both sides of the corpus callosum. Between April and June 2013, he was treated with three cycles of TMZ (5/23-day protocol). In June 2013, MRI detected PD and in the same month he underwent re-RT with 39 Gy (5×3 Gy/week). The first 250 mg CQ dose was administered 3 days before starting re-RT and the patient took CQ daily during re-RT and thereafter until August 2013 when rapid clinical deterioration was observed. At his own request, tumor-specific therapy was discontinued and he died in December 2013.

Patient 5

In August 2012, a 54-year-old male patient was diagnosed with GBM (WHO IV) of the left frontal lobe. In the same month, he was operated and between September and October 2012, he was treated with RCHT according to the EORTC 26981/22981-NCIC CE3 protocol [14]. Until April 2013, six cycles of adjuvant TMZ chemotherapy were administered. In June 2013, MRI revealed PD and in the same month the recurrent tumor was resected. Postoperative MRI and FET-PET/CT did not detect any residual tumor. Considering that the tumor was very small (ca. 1 cm maximal diameter), the surgical cavity was reirradiated with 50 Gy (5×2 Gy/week) between July and August 2013. On the first day of re-RT and 6 weeks later he received 80 mg/m^2 CCNU. The first 250-mg CQ dose was administered 3 days before starting re-RT and the patient took CQ daily during and after re-RT. In the first follow-up (November 2013) he presented to our clinic in excellent condition (ECOG 0) and MRI did not show any sign of PD. He is still continuing to take CQ daily and CCNU every 6 weeks.

Discussion

To the best of our knowledge, this is the first report of an innovative therapeutic strategy using PET-based re-RT in combination with CQ in patients with rGBM.

Abstract · Zusammenfassung

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FET-PET-based reirradiation and chloroquine in patients with recurrent glioblastoma. First tolerability and feasibility results

Abstract

Background. Treatment of recurrent glioblastoma (rGBM) remains an unsolved clinical problem. Reirradiation (re-RT) can be used to treat some patients with rGBM, but as a monotherapy it has only limited efficacy. Chloroquine (CQ) is an anti-malaria and immunomodulatory drug that may inhibit autophagy and increase the radiosensitivity of GBM.

Patients and methods. Between January 2012 and August 2013, we treated five patients with histologically confirmed rGBM with re-RT and 250 mg CQ daily.

Results. Treatment was very well tolerated; no CQ-related toxicity was observed. At the first follow-up 2 months after finishing re-RT, two patients achieved partial response (PR), one patient stable disease (SD), and one patient progressive disease (PD). One patient with reirradiated surgical cavity did not show any sign of PD.

Conclusion. In this case series, we observed encouraging responses to CQ and re-RT. We plan to conduct a CQ dose escalation study combined with re-RT.

Keywords

Reirradiation · Chloroquine · Glioblastoma multiforme · Radiosensitivity · Recurrence

FET-PET-basierte Rebestrahlung und Chloroquin bei Patienten mit rezidiviertem Glioblastom. Erste Ergebnisse zu Toleranz und Durchführbarkeit

Zusammenfassung

Hintergrund. Die Behandlung rezidivierter Glioblastome (rGBM) ist problematisch. Manche Patienten können erneut bestrahlt (re-RT) werden, jedoch nur mit begrenzter Wirksamkeit. Das Antimalariamittel Chloroquin (CQ) wirkt immunmodulatorisch, hemmt die Autophagie und kann die Radiosensibilität erhöhen.

Ergebnisse. Zwischen Januar 2012 und August 2013 wurden 5 Patienten mit einem histologisch gesicherten rGBM mit re-RT und zusätzlich täglich 250 mg CQ behandelt. Diese Behandlung wurde sehr gut, ohne CQ-assoziierte Nebenwirkungen toleriert. Zum ersten Follow-up, 2 Monate nach der re-RT, fanden sich zwei partielle Remissionen (PR), ein stabiler Verlauf (SD) und ein Progress (PD). Ein zuvor operierter Patient war in anhaltender Remission.

Schlussfolgerung. Diese Fallstudie zeigt ein ermutigendes Ansprechen von Patienten mit rGBM auf eine Behandlung mit CQ und re-RT. Eine Dosiseskalationsstudie CQ/re-RT ist geplant.

Schlüsselwörter

Rebestrahlung · Chloroquin · Glioblastom · Radiosensibilität · Rezidiv

Table 1 Patient characteristics

Patient no.	ECOG	MGMT methylation status	PTV (cm^3)	CQ intake (months)	Survival after finishing re-RT (months)
1	1	Methylated	67 and 6.5	17	23+
2	3	ND	34.9	12	13
3	1	ND	27.9	5.5	5.5
4	3	Unmethylated	118.1	3	5
5	0	Unmethylated	20	5+	5+

ECOG Eastern Cooperative Oncology Group, **ND** not determined, **PTV** planning target volume, **CQ** chloroquine, **re-RT** reirradiation

The treatment was well tolerated by all five patients in our study and no side effects related to CQ were observed.

In this population, one of the patients had two lesions, in two patients the tumor infiltrated the corpus callosum, and in one patient the tumor was inoperable at the time of the first diagnosis. Despite large tumors in unfavorable locations, good responses to treatment were observed. Three patients continued to take CQ with other chemo- or antiangiogenic therapies (bevacizumab, CCNU, TMZ) and we did not record any additional toxicity that may be related to the use of CQ.

CQ is an inexpensive, easily available, well-tolerated drug with few side effects that has been used extensively in the treatment of malaria and rheumatic diseases. Despite considerable basic scientific evidence for antineoplastic and radiosensitizing effects of CQ and a well-known pharmacological profile, there are few published results about the usefulness of CQ in patients with neoplastic disease. To date, only results from three clinical studies and three case reports have been reported. In one clinical trial, in patients with primary diagnosed GBM, the combination of RT and CQ was well tolerated; no severe side effects were observed [17]. Despite encouraging results on survival (24 months with CQ vs. 11 months without CQ, not significant), this study has some limitations. Due to the small number of patients ($n = 15$ in each group), differences in pretreatment characteristics and conventional treatment regimens could not be adjusted.

In two other trials [1, 15] in patients with brain metastases, CQ was administered during whole-brain irradiation. No patient suffered from CQ-related toxicity.

However, in three case reports severe skin toxicity was observed. Rustogi et al. treated a 12-year old girl with a pontine glioma with RT [16] (cobalt-60 γ-ray unit, total dose of 54 Gy in 30 fractions). Due to suspected malaria, empirical treatment with CQ was started. She received 750 mg CQ once and two additional daily doses of 250 mg after 36 Gy. A severe skin desquamation was observed 3 days after the third CQ dose. In two other case reports [12, 19] the authors describe side effects of breast/chest wall RT in patients with breast cancer who took parallel CQ due to malaria or rheumatoid arthritis. In all three reported cases, the authors concluded that the observed increased tissue toxicity was the consequence of CQ intake. Notably, all these patients were treated with a higher single CQ dose or CQ was used for a longer time.

In all reported cases, a cobalt-60 γ-ray gamma irradiation source was used, which today is not a state-of-the-art technique. On the other hand, these effects may also be the consequence of an individually enhanced sensitivity toward RT.

There are no published data on the usefulness of re-RT and CQ in any neoplastic disease. In this case series, 250 mg CQ orally in combination with re-RT was well tolerated. Based on this fact and our previous observation that CQ increased the apoptotic cell death of stem-like glioma cells induced by IR in a concentration-dependent manner [2], we plan to start a dose escalation phase I study using higher CQ doses in combination with re-RT.

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Compliance with ethical guidelines

Conflict of interest. A. Bilger, M.-I. Bittner, A.-L. Grosu, N. Wiedenmann, P.T. Meyer, E. Firat, G. Niedermann, W.A. Weber, and D. Milanović state that there are no conflicts of interest.

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