Changes in blood-brain barrier permeability induced by radiotherapy: Implications for timing of chemotherapy? (Review)

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Abstract. The brain requires a stable internal environment, which is established by the integrity of the blood-brain barrier (BBB). The efficacy of chemotherapeutics in the treatment of brain malignancies is often hampered by the presence of the BBB. BBB disruption can be performed either by osmotic disruption, bradykinin or irradiation. Radiotherapy with doses of 20 to 30 Gy with fraction size of 2 Gy may be used to increase the permeability of the BBB. These radiation doses by themselves will not give rise to serious side effects or long-term complications. Disruption of the BBB by radiotherapy might have implications in the treatment of primary brain tumors, cerebral metastases, and prophylactic cranial irradiation in small cell lung cancer since irradiation will cause cell kill and may enhance the effect of chemotherapy. We present a review on the effects of irradiation on the BBB and subsequently discuss the potential value for therapeutic applications.

Contents

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1. Introduction

The brain requires a stable internal environment, which is established by the integrity of the blood-brain barrier (BBB). A stable environment is needed especially to ensure optimal functioning of the neurons. The BBB is situated in the endothelium of cerebral microvessels. These bloodvessels are much less permeable for large molecules than those elsewhere in the body (1). The permeability of the BBB is regulated dynamically by special features like hormones and narrow tight junctions between the endothelial cells (2). Environmental, physiologic and psychologic factors may influence the permeability of the BBB (3).

Most malignant tumors produce angiostimulating factors, which cause vascular proliferation in and around the tumor (4). The permeability of these capillaries is increased compared to those of normal capillaries, as evidenced by contrast enhancement of tumor visualized on CT or MR images (5). However, although tumor vessels may be 'leaky', the increase in permeability in both experimental and human tumors is modest. The brain-tumor barrier is still generally considered to be restrictive with respect to the transcapillary flux of most water soluble compounds (6). Qin *et al* noted that the BBB permeability in and around brain tumors is only about 20% more than in normal brain tissue (7).

The efficacy of most chemotherapeutic agents is hampered by a normal BBB. Some agents, like nitrosoureas, can easily pass the BBB (8). Alternative ways of administering chemotherapeutics have been investigated, like intrathecal administration, but this has no effect on brain tumors in the parenchym (9). An impaired functioning of the BBB may lead to an increased efficacy of chemotherapeutic agents. Temporary osmotic damaging of the BBB, e.g., by mannitol (10-15) and Cereport, a novel bradykinin agonist (16,17), have been applied for treating brain tumors with chemotherapy. Irradiation has also been shown to disrupt the BBB (7,18-24), but is, up till now, hardly used for this purpose.

We here present a review about the effects of irradiation of the BBB and subsequently we will discuss the potential value and implications of therapeutic applications. We employed Medline for the search of relevant references with the key words blood-brain barrier, radiotherapy/irradiation, and chemotherapy.

2. BBB and irradiation

Several methods have become available in the past two decades to quantify BBB damage. Measurements have been performed using radioactive markers (7,18,25,26), dynamic MRI with or without contrast (27), dynamic CT-scan (23), immunohistochemistry (28), PET scan, IgG (19,29,30), albumine (19,29) and methotrexate (MTX) concentration in cerebrospinal fluid (CSF) (21,22), or after I-125 cerebral implantation (24). Several investigations were done with regard to boron-neutron capture therapy (31,32). Results on BBB damage induced by irradiation can be summarized as follows.

Changes in the BBB of experimental animals. Rats have been exposed to conventionally fractionated irradiation, 20 times 2 Gy, 5 times a week, to the brain. By measuring the concentration of the radioactive marker 14C- · aminoisobutyric acid in and around the vessels, a rise of the marker outside the bloodvessels was observed two weeks after whole brain irradiation. Three months after irradiation well-defined alterations in the microvasculature were still noted (25,26).

Krueck *et al (27)* assessed the potential of T1-weighted, gadolinium-enhanced MR technique for quantifying radiation-induced changes of BBB in a model of intracerebral gliomas in rats. Rats were treated with whole-brain irradiation of 15 and 25 Gy and increased BB permeability was observed. They concluded that contrast-enhanced dynamic MR of brain gliomas is a sensitive method to document BBB break-down.

Nakata *et al (28)* studied the effect of high single dose irradiation of 20 and 40 Gy on the permeability of BBB in rat brains. Immunohistochemistry with an antibody to serum albumin was used as a sensitive method for extravasation of endogenous serum components. Immunoreactivity reached its maximum after 3 days and had disappeared by day 30.

Storm *et al* (33) administered MTX i.v. in WAG/Rij rats 1 to 15 days after a single dose of 20 Gy of 300 kV X-rays to the brain. This resulted in a significant increase in MTX as determined by ^{125}I-radioimmunoassay in the irradiated rat brain tissue. However, MTX concentration in serum and brain tissue of young rabbits was not influenced significantly 4 and 14 weeks after fractionated doses of 24 Gy (22).

After intracerebral iodine-125 implantation of normal dogs a sharp-lined barrier destruction could be seen, which continued for one year and returned to normal levels after 2 years (24). The BBB function was measured with carbon-14 labeled · aminoisobutyric acid and quantative autoradiography.

The combination of intracerebral administration of bleomycin and irradiation to rats bearing the experimental 9L gliosarcoma was more effective than either modality alone (20).

A tendency towards increased boron uptake in the moderately BNCT (boron-neutron capture therapy) treated brains was noted indicating alteration of the BBB (31).

Changes in the BBB of patients. Qin *et al (7)* showed in a pilot study in 14 patients by $99^{m}T_{C}$ GH imaging that the destruction of the BBB in irradiated normal brain tissue showed a linear relation with radiation dose. Cerebral tissue that was not irradiated, e.g., just next to the radiation field, showed no altered function of the BBB. In case of a malignant brain tumor the BBB permeability in and around the tumor was approximately 20%. After administering a total dose of 30 Gy the permeability was 75%. Measuring permeability after 8 months revealed that the permeability of the BBB in the tumor had returned to pre-treatment levels. In normal tissue the BBB recovered completely.

After irradiation of the brain with a dose of 20 Gy and intravenous administration of MTX to patients with brain tumors, the CSF-MTX concentration increased up to threefold (34). Therefore, Qin *et al* advised starting chemotherapy only after irradiation with doses of 20 Gy to the brain (34). Qin *et al* (35) retrospectively analysed the outcome of 56 glioblastoma patients. Their study confirmed that opening of the BBB by irradiation with total doses administered at 2 Gy per fraction may optimise the effects of intracranial chemotherapy.

Jarden *et al* (18) performed dynamic positron emission tomographic measurement of blood-to-brain and blood-to-tumor transport of 82Rb in patients with metastatic brain tumors, treated with a dose of 2 to 6 Gy to the whole brain. Patients also were treated with dexamethasone. They reported that steroid pretreatment prevents acute increases in tumor capillary permeability following cranial irradiation.

Tellkamp and Kohler (23) employed dynamic CT in the follow-up assessment of patients irradiated for intracranial tumors. They concluded that dynamic cerebral CT is a sensitive method for assessing tumor vascularisation and for assessing a disturbance of the BBB.

An increase of albumin concentration in CSF was noted after radiotherapy of the brain for acute lymphoblastic leukaemia (19). This was seen as proof of radiotherapy destructing blood-CSF barrier. This was also noted for the BBB after central nervous system (CNS) irradiation to multiple sclerosis patients (29) and to children with acute lymphoblastic leukaemia (21).

From these methods to investigate and quantify BBB disruption we conclude that irradiation caused increased permeability of the BBB.

3. BBB disruption by osmotic agents

Osmotic agents, such as mannitol (36,37) and Cereport (or RMP-7) (16,17,28) can cause BBB disruption. Osmotic opening of the BBB by mannitol solution is mediated by vasodilatation and shrinkage of cerebrovascular endothelial cells, with widening of the interendothelial tight junctions. Osmotic BBB disruption has been applied in patients with metastatic or primary brain tumors (29,30). In a National Blood-Brain Barrier Program over 4200 BBB disruption procedures have been performed in more than 400 patients (14). In these patients enhanced delivery of chemotherapy resulted in high response rates (13) without loss of cognitive function (15). Remsen *et al (39)* used osmotic BBB disruption in a rodent human lung cancer brain xenograft model and reported enhanced delivery of immunoconjugates. Barth *et al* (40) and Yang *et al (41)* observed enhanced survival and cure of rats bearing intracerebral F98 glioma. Rats were treated with boron neutron therapy. Enhanced delivery of boronophenylalanine following BBB disruption by mannitol or Cereport was noted.

Ionising radiation has also been used to increase the permeability of the BBB and may thereby enhance the chemotherapeutic response. The radiation dose itself will cause about 3-4 log cell kill when doses of 20 to 30 Gy are applied. In contrast to irradiation, mannitol or Cereport itself will not cause tumor cell kill.

From literature it is clear that BBB disruption can be obtained either by mannitol, Cereport or by irradiation. Irradiation with a dose of 20 to 30 Gy has the advantage of reducing cell number by a factor of about 10^3 to10^4.

4. Time to BBB recovery

To make advantage of an impaired functioning of BBB after irradiation, e.g., for administration of chemotherapeutic drugs or radioprotectors, it is important to know the length of the period during which the BBB is disrupted. In literature various results are described.

Experimental animals. Rat brains have been exposed to a regimen consisting of 20 dose fractions of 2 Gy, 5 times a week (25,26). Three months after irradiation well defined alterations in the microvasculature were still observed.

Using quantitative autoradiography, the blood-to-tissue constant of ^{14}C-·-aminoisobutyric acid (AIB) was measured in rat gliomas in brains. The AIB transport data suggest that vascular permeability increases significantly on the day following a single dose of 20 Gy. This increase reverses by the second day following irradiation (42).

Groothuis *et al (24)* also measured BBB function with AIB and quantitative autoradiography in canine brain. They reported well-defined changes in BB function that may persist for over one year following insertion of ^{125I} seeds.

Immunohistochemistry with an antibody to serum albumin was used as a method for detecting the extravasation of endogenous serum components. Extravasation of albumin in rat brains was detected as early as 1 day after irradiation with single doses of 20 or 40 Gy. Immunoreactivity reached its maximum after 3 days, gradually decreased during the following weeks, and had disappeared by day 30. This transient impairment of BBB may allow drugs that normally not pass the BBB to do so (28).

Patients. Disruption of the BBB in patients was noted by Chan *et al (43)* and Qin *et al (35)*. Chan *et al* studied morphologic characteristics of late radiation injury to the temporal lobes of the brain on magnetic resonance images. Patients were treated 2-10 years before for nasopharyngeal carcinoma. Blood-brain barrier disruption based on parenchymal contrast enhancement was observed in 89% of the patients. Thus, even 2-10 years after radiotherapy, BBB disruption could still be observed.

Qin *et al* (35) concluded from a retrospective study that radiation doses administered with 2 Gy-fraction dose produced maximal opening of the BBB for more than half a year.

In summary, the time to recovery of the BBB varies in literature from several hours to several years.

5. Toxicity of brain irradiation

DeAngelis *et al (44)* described 12 patients developing severe dementia after whole brain radiotherapy (WBRT). The total dose of WBRT was only 25-39 Gy, however, relatively large daily fractions of 3 to 6 Gy were employed. The incidence of WBRT-induced dementia was 1.9 to 5.1% in the two populations reviewed. They believed that these fractionation schedules, several of which are used commonly, predispose to delayed neurologic toxicity, and that more protracted schedules should be employed for the safe and efficacious treatment of good-risk patients with brain tumors or brain metastases.

Taphoorn *et al (45)* concluded that local irradiation with total doses of 45 to 63 Gy of low-grade glioma patients does not cause cognitive damage or impaired quality of life. In three other prospective studies no cognitive damage or other adverse neurologic effects of prophylactic cranial irradiation (PCI) for patients with small cell lung cancer (SCLC) were noted when low fraction doses (2-3 Gy) were used and total doses did not exceed 30 Gy (46-49).

From these findings it can be concluded that adverse side effects of schemes using a 2 Gy fraction size and a total dose of 30 Gy are not to be expected. In addition, this total dose is far below the tolerance dose of 45 to 60 Gy for brain tissue, depending on the volume treated (50).

6. Toxicity of combined chemoradiotherapy

Most reports on toxicities of a combined chemo-radiation course describe acceptable side effects (51-53). However the incidence of long-term side effects is in many series not well known, and it is likely that an under-estimation exists (54). The magnitude of toxicity depends on the age and condition of the patient, which chemotherapeutic agent is used, how and in what dose it is administered, the radiation dose, fraction size, field size and in which order the radiochemotherapy is performed: concomitant, or sequential (54). Considering treatments with radiation-induced BBB disruption for the purpose of optimal chemotherapy, toxicity studies will have to be performed first.

7. Protection of BBB from radiation-induced damage

Irradiation can result in an acute increase of oedema, for which corticosteroids are frequently prescribed. Corticosteroids reduce capillary permeability for small molecules and may contribute in reducing inflammation (18). This explains the use of dexamethasone in reducing complaints caused by oedema in brain tumors. Albumin concentration in CSF is transiently increased after radiotherapy, but when patients received ACTH/prednisolone no damage to the BBB was found (29). Thus, recovery of BBB damage induced by irradiation can be obtained by administering corticosteroids (18,29,55). Therefore, it is questionable to administer dexamethasone to a brain tumor patient treated with chemotherapy and radiotherapy since the efficacy of the combined treatment modality might decrease.

8. Clinical application of BBB disruption by irradiation

BBB disruption by irradiation has the advantage that irradiation will cause cell kill and may enhance the effect of chemotherapy. One study suggests that, in order to increase the permeability of the BBB by irradiation, a total dose of 20 to 30 Gy with fractions sized up to 3 Gy are needed (7). To reduce long-term toxicity a maximum fraction size of 2 Gy is preferable (56). The study of Qin *et al* (35) confirmed that opening of the BBB by irradiation with total doses administered at 2 Gy per fraction may optimise the effects of intracranial chemotherapy.

These radiation doses will not give rise to serious side effects or long-term complications. These findings should be taken into account considering radiotherapy to open the BBB. Radiation-induced BBB disruption may be considered for the treatment of primary brain tumors, e.g., gliomas, prophylactic cranial irradiation in small cell lung cancer (SCLC) and cerebral metastases.

High-grade gliomas are usually treated by (postoperative) radiotherapy. The prognosis is dismal; the 2-year survival is only 5-10% (57,58). Studies on the efficacy of chemotherapy alone show hardly any benefit (44,59). Delivering the chemotherapeutic drugs to the target area is a major problem due to the BBB. Intra-arterial application of chemotherapy for patients with glioblastoma multiforme, delivered prior to radiation therapy, appears to result in a median survival three times longer than that achieved with concomitant chemotherapy/radiation therapy (53). They concluded that the best treatment is intra-arterial chemotherapy with cisplatin and etoposide given prior to radiation therapy with doses in the range of 61 to 63 Gy administered with a fraction dose of 1.8 Gy. Not explored was the sequence radiotherapy followed by chemotherapy. New developed drugs such as temozolomide, a second-generation alkylating agent, may be promising (60). Recently an EORTC study (EORTC 26981) on temozolomide and concomitant radiotherapy has started (61). A combination of radiation therapy also with the intention to disrupt the BBB followed by chemotherapy may improve treatment results.

The same goes for low-grade gliomas. Ten year local control after surgery and radiotherapy is 30-40%. Low-grade gliomas are known to respond to irradiation although long-term results are disappointing and the role of early radiotherapy in these patients is debatable (Karim ABMF, *et al*, J Neurooncol 39: abs., p101, 1998). A combination of radiotherapy followed by chemotherapy might improve long-term treatment results.

The risk of developing brain metastases in limited disease SCLC increases with length of survival to a cumulative risk of 80% at two years (57,58). Recently, a survival benefit after prophylactic cranial irradiation (PCI) versus no PCI for SCLC in complete remission has been demonstrated in a meta-analysis concerning 987 patients (62), but treatment results are still far from optimal. They also identified a trend toward a decrease in the risk of brain metastasis with earlier administration of cranial irradiation after the initiation of induction chemotherapy. A logical next step would be to investigate the administration of PCI in between the chemotherapy courses. The effect on cerebral micrometastases of such a combined treatment will probably be better than of PCI after chemotherapy courses, knowing the sensitivity of SCLC to chemotherapy. The complication rate of the combined treatment has to be assessed.

Cerebral metastases are usually treated by radiotherapy alone. Median survival after radiotherapy alone is only 3.6 months (63). To search for improvements, the application of a novel radiosensitizing agent Motexafin gadolinium, also known as gadolinium texaphyrin, is now studied in a phase III clinical study after multicenter phase Ib/II trial (64). However, in case of chemosensitive tumors, e.g., breast carcinoma, an additive effect may be expected by a combined treatment with radiotherapy followed by chemotherapy. Complications of this combined treatment have to be investigated.

10. Conclusion

Oncology today tends increasingly to be a multimodality treatment. Also in case of primary brain tumors, PCI and cerebral metastases the possible combination of (post-operative) radiochemotherapy has to be investigated in which the radiotherapy is the modality to diminish tumor burden, and has the advantage to disrupt the BBB for a more effective application of the chemotherapy.

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