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Abstract: The long-term treatment of peritumoral edema remains a major challenge in clinical neuro-oncology. Steroids have been and will remain the backbone of any anti-edematous therapy because of their striking activity, convenient oral administration and also because of their cost-effectiveness. Their side effects, however, can compromise quality of life, particularly upon continuous administration. Therapeutic alternatives which may replace or - at least - help to reduce the steroid dose are limited. However, with the development of new agents such as corticorelin acetate, there is a hope that steroid-induced side effects can be delayed and reduced. The administration of anti-angiogenic agents with steroid-sparing effects, for example, bevacizumab, is limited due to their costs. Increased knowledge on boswellic acids and cyclooxygenase-2 inhibitors which are available for clinical application may help to exploit their anti-edema activity more efficiently in the future.

Tumor-associated edema in brain cancer patients: pathogenesis and management

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Summary

The long-term treatment of peritumoral edema remains a major challenge in clinical neurooncology. Steroids have been and will remain the backbone of any anti-edematous therapy because of their striking activity, convenient oral administration and also because of their cost effectiveness. Their side effects, however, can compromise quality of life, particularly upon continuous administration. Therapeutic alternatives which may replace or – at least – help to reduce the steroid dose are limited. However, with the development of new agents such as corticorelin acetate, there is hope that steroid-induced side effects can be delayed and reduced. The administration of anti-angiogenic agents with steroid-sparing effects, e.g. bevacizumab, is limited due to their costs. Increased knowledge on boswellic acids and COX-2 inhibitors which are available for clinical application may help to exploit their anti-edema activity more efficiently in the future.

Background

Peritumoral edema is a typical finding of malignant neoplasms of the central nervous system (CNS) such as high-grade gliomas and metastases. It can, however, occur in virtually any CNS neoplasm including World Health Organization (WHO) grade I meningiomas, which are among the most common benign brain tumors. Rare subtypes of benign meningiomas such as angiomatous, microcystic and secretory meningioma may be associated with prominent perifocal edema. The presence of edema, therefore, is not a direct indicator of malignancy [1]. Therapeutic interventions on the tumor such as surgery, irradiation or chemotherapy may influence edema evolution [2-4]. Tumor-associated edema significantly contributes to the mass effect of CNS neoplasms and neurological deterioration. The pathophysiological mechanisms leading to the development of edema have been stepwise characterized in the last decades. The improved understanding of the molecular determinants underlying edema formation is a prerequisite for the development of novel therapeutic agents with anti-edema activity.

Pathogenesis

Peritumoral edema does not necessarily represent a single entity but may differ regarding their pathogenesis between meningiomas, gliomas and metastases. However, several basic mechanisms have been described as hallmarks of peritumoral edema. Similar to edema associated with abscess, tumor-related edema is considered to be vasogenic, that is, disturbed blood-brain barrier function resulting in increased vascular permeability. The altered vascular architecture in brain tumors results in loss of the barrier function and allows for a leakage of plasma fluid and proteins into the surrounding tissue [5]. Such a dysfunctional blood-brain barrier is found in high-grade gliomas but also many other malignant brain tumors.
Tumor cells typically produce various cytokines which act on endothelial cells located within or around the tumor. Among others, the most important cytokine secreted by various brain tumors is *vascular endothelial growth factor* (VEGF) [6]. VEGF has initially been described as *vascular permeability factor* indicating that it is one of the most potent mediators of vascular permeability [7,8]. Under the influence of VEGF, the permeability of endothelium is increased resulting in a disturbance of the blood-brain barrier [9,10]. Tumor-derived VEGF may also enhance blood flow and induce vasodilatation [11]. It binds to different receptors

which are expressed by endothelial cells and also acts as a critical driver of angiogenesis in various neoplasms [12]. In many tumors such as gliomas, VEGF levels correlate with the grade of malignancy [13]. In meningiomas, the occurrence of brain edema is associated with increased VEGF levels which may contribute to edema evolution [14-16]. Similar mechanisms are present in metastatic brain tumors. They also release angiogenic factors acting on endothelial cells and promoting capillary formations characterized by various abnormalities.

Besides VEGF, other factors which may be involved in the evolution of peritumoral edema comprise arachidonic acid metabolites and nitric oxide (NO). Increased leukotriene C4 expression was noticed in brain tumors and may contribute to edema development by increasing the blood-brain barrier permeability [17]. Furthermore, the microenvironment surrounding brain tumors may also participate in the evolution of edema. Microglial cells infiltrating brain tumors are characterized by high expression levels of cyclooxygenase-2 (COX-2) which generates prostaglandin E2 (PGE2). COX-2 is also expressed by glioma cells [18,19]. COX-2-derived PGE2, in turn, may promote the growth of experimental gliomas and contribute to edema development [20,21]. Similar mechanisms have been claimed for meningioma-associated edema [22]. VEGF-mediated NO expression through induction of endothelial nitric oxide synthase (eNOS) can promote vasodilation in brain tumors [23]. NO production in tumor endothelial cells may subsequently contribute to edema formation but its exact role has not been clarified [24,25].

Tumor vessels are characterized by fenestrations and pathological tight junctions [26,27]. Various molecules which contribute to the function of tight junctions such as claudins and occludin are down-regulated on tumor microvessels [28,29]. Intracellular molecules including Zonula Occludens (ZO)-1 and ZO-2 mediate an interaction of tight junction proteins with the endothelial cell cytoskeleton. Reduced expression levels of these proteins preclude appropriate function of tight junctions and results in fluid extravasation and evolution of edema. Furthermore, the functional activity of occludin and ZO-1 may be impaired by VEGF which subsequently translates into an opening of tight junctions [30].

Is has also been reported that increased glutamate levels secreted via the xCT transporter which is expressed by glioma cells contribute to the formation of peritumoral edema. Pharmacological or genetic inhibition of the xCT transporter resulted in a reduction of edema and prolonged survival of glioma-bearing rats [31]. Additional molecules which may be involved in the development of peritumoral edema include the family of aquaporins (AQP), a group of water channel proteins. AQPs are integral membrane proteins that are broadly

expressed in many cells. They are involved in the control of water flow into and out of cells [32]. AQP1 is overexpressed in tumor microvessel endothelia as well as glial and metastatic tumor cells [33]. In a similar study, increased AQP4 levels were observed in high-grade astrocytomas and brain metastases [34]. These authors noticed a correlation between blood-brain barrier opening and increased AQP4 levels. AQP4 upregulation is also associated with brain edema formation in malignant gliomas [35]. Furthermore, AQP4 protein levels correlate with VEGF expression levels in gliomas [36]. AQP5 is highly expressed in meningiomas and correlates with the intensity of edema [37]. As a consequence, the upregulation of AQP family members may be implicated in the flow of edema fluid. However, their exact role in the evolution and persistence of peritumoral edema needs further investigation.

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Management of edema.

Steroids

Vasogenic edema typically responds very well to corticosteroid treatment. Therefore, steroids are the most frequently used agents for the treatment of brain tumor-surrounding edema. The first reports, published in the 1950s, suggested a beneficial effect on the outcome of patients undergoing brain tumor surgery when cortisol or other drugs with glucocorticoid activity were administered perioperatively [38,39]. The availability of synthetic steroids such as prednisone or dexamethasone resulted in a rapid and widespread use of these agents in brain tumor patients. The mode of action of steroids, their clinical use as well as their important side effects have recently been reviewed in detail [40,41]. Therefore, the following section represents only a brief summary on some of the most important aspects of steroids as anti-edematous agents. Dexamethasone is used by most neurooncologists because of its high glucocorticoid potency which is required for anti-edema therapy, hardly any mineralocorticoid side effects and a long biological half-life in the range of 48-54 h allowing for a daily single-dose administration. Hardly any data from placebo-controlled trials assessing the efficacy of steroids on the tumor-surrounding edema in brain tumors are available. However, there is not doubt on their distinct anti-edema activity resulting in a wide-spread use all over the world. After administration, corticosteroids may result in rapid relief from neurological symptoms due to the reduction of the edematous mass. This effect, however, is typically transient and diminishes within weeks or months. Furthermore, the use

of steroids may be associated with significant toxicity precluding their unrestricted use. The most frequent acute side effects associated with the administration of steroids include hyperglycemia and arterial hypertension. Long-term intake frequently results in the development of osteoporosis, myopathy, psychiatric alterations, skin thinning and an increased risk for some opportunistic infections. Furthermore, steroids may reduce the sensitivity of tumor cells, other than lymphoma cells, to chemotherapeutic agents. Corticosteroids may also interfere with the metabolism of other therapeutics such as anticonvulsants, and vice versa. Therefore, steroid administration should be minimized whenever possible. However, despite these limitations, glucocorticoids remain the most important component in the treatment of peritumoral edema in brain cancer patients.

Corticorelin acetate

Human corticotropin-releasing factor (hCRF) is a naturally occurring neuropeptide which is produced in the hypothalamus [42]. It regulates the release of adrenocorticotropin hormone (ACTH) from the pituitary gland which subsequently induces hydrocortisone liberation from the adrenal gland. There are 2 hCRF receptors, CRF1 and CRF2, which are also expressed by numerous tumor cells [43]. Data from experimental glioma models suggest that hCRF may decrease tumor vascular permeability and vasogenic edema *in vivo* [44,45]. In these experiments, hCRF decreased the peritumoral edema also in adrenalectomized animals, pointing to a mode of action independent of the release of corticosteroids. It has been speculated that the anti-edematous effect of hCRF is due to a direct action on the microvasculature [46]. A phase I trial of hCRF in patients with peritumoral brain edema indicated that the drug is well tolerated when administered as a continuous infusion. Ten out of 17 patients experienced improvement of neurological symptoms whereas rather minor effects on the edema were observed by magnetic resonance imaging (MRI). Clinical improvement did not correlate with changes in cortisol levels [47]. Corticotropin acetate (CrA, Xerecept) is a synthetic analog of hCRF. When administered to glioma-bearing nude mice, it resulted in prolonged survival compared to dexamethasone- or temozolomide-treated animals [48]. The combination of CrA with bevacizumab in a rodent glioma model was associated with prolonged survival compared to either drug alone [49]. A prospective, randomized, double-blind study of 200 patients with primary and secondary brain tumors assessed the putative steroid-sparing effect of CrA. All patients had to be on a stable steroid

dose at enrolment. Patients within the CrA group received subcutaneous injections of 1 mg of the drug twice daily. CrA was well tolerated with injection site reactions as the only adverse event that was more prevalent in the CrA group. The primary end point, a reduction of the dexamethasone dose by 50% or more without worsening of neurological symptoms or performance status, showed a trend in favor of the CrA group without reaching statistical significance (p=0.12). However, the maximum percent reduction of the dexamethasone dose was more pronounced in the CrA group (62.7%) than in the control group (51.4%, p<0.001). Furthermore, patients receiving CrA were less frequently affected by myopathy and less likely to experience Cushingoid appearance [50]. Overall, these results are promising and CrA may represent a novel option allowing for a reduction of steroid administration in some patients. However, the steroid-sparing effects of CrA need further investigation. Future trials should define whether CrA administration may allow for a complete replacement of glucocorticoids in patients requiring only small steroid doses.

Anti-angiogenic agents

As outlined above, the abundant expression of VEGF in various brain tumors which are typically associated with significant perifocal edema has been recognized about 20 years ago [51]. In contrast, tumors which commonly lack large edemas such as pituitary adenomas are characterized by lower VEGF expression. Owing to its implication in the development of peritumoral edema, inhibition of VEGF signaling has been regarded as a promising therapeutic strategy for a long time. However, only within the last years, various agents targeting the VEGF pathway have become widely available.

Bevacizumab is a humanized monoclonal antibody against VEGF-A which has been approved by the FDA for treatment of recurrent glioblastoma. In glioblastoma patients, bevacizumab administration frequently causes a distinct reduction in edema which is commonly associated with a reduction or even complete cessation of steroid administration [52,53]. MR imaging frequently demonstrates a reduction of peritumoral edema upon bevacizumab administration [54]. However, owing to its cost and the lack of approval in this indication, bevacizumab cannot be considered an alternative to steroids. Another agent which has been developed within the last years is the pan-VEGF receptor tyrosine kinase inhibitor cediranib. In a rodent glioma model, cedarinib prolonged survival of tumor-bearing mice due to its anti-edema action without inhibiting the growth of tumor cells proper [55]. Cediranib has also shown

efficacy in normalization of tumor vessels in recurrent glioblastoma patients and reduction of peritumoral edema [56]. A steroid-sparing effect of cediranib was also reported in a further series of patients with progressive glioblastoma [57]. However, the failure of the compound to prolong progression-free survival in a phase III study in patients with recurrent glioblastoma (NCT00777153), administered either alone or in combination with lomustine, has questioned the clinical activity of the compound [58]. Other novel agents targeting the VEGF pathway such as pazopanib, a multikinase angiogenesis inhibitor may be active against brain tumor-surrounding edema but must currently be considered as an experimental approach in neurooncology [59].

Boswellic acids

Boswellic acids, phytotherapeutic agents which are obtained by extraction from *boswellia serrata*, have been assessed for their anti-inflammatory properties and as putative anti-cancer drugs for many years. Boswellic acids are cytotoxic to glioma cells *in vitro* at low micromolar concentrations [60]. Furthermore, anti-edematous action has been described in a small series of brain tumor patients undergoing radio- or chemotherapy treated with the boswellia preparation H15 [61,62]. More recently, within a prospective trial 44 patients with primary or secondary malignant cerebral tumors were randomly assigned to receive radiotherapy plus either H15 or placebo. A reduction of cerebral edema of >75% assessed by T2-weighted MRI was observed in 60% of patients treated with H15 compared to 26% of patients receiving placebo (p=0.023). H15 was well tolerated except for minor gastrointestinal side effects in some patients. There was no significant difference in dexamethasone dose between the 2 groups. Furthermore, treatment with H15 had no significant impact on quality of life or cognitive function [63]. The exact mode of action of boswellic acids on peritumoral edema has remained unclear but may partially rely on an interference with the VEGF pathway and suppression of PGE2 formation [64,65]. Overall, larger studies are required to assess the potential steroid-sparing effects of boswellic acids and their impact on therapy-related edema in more detail. Furthermore, a better understanding of the molecular mechanisms underlying the functional activity of boswellia extracts may help to exploit their full therapeutic potential.

COX-2 inhibitors

COX-2 may contribute to the evolution of tumor-related edema as outlined above. Drugs which target COX-2 are widely available and have been partially assessed for their anti-edematous efficacy. Celecoxib reduced VEGF expression levels in a preclinical tumor model [66]. The specific COX-2 inhibitor SC-236 was assessed in a rat brain tumor model and had a similar effect on survival than dexamethasone [67]. Rofecoxib inhibited the leakage of contrast medium in glioma-bearing rats to a similar amount as dexamethasone [20]. Whether these effects also occur in human patients and translate into clinical benefit has not been examined in detail. Case reports suggest a certain anti-edematous activity of COX-2 inhibition but confirmation in larger series is pending [68].

Other agents

Osmotherapeutic agents such as mannitol, glycerol, or hypertonic saline are frequently used in patients suffering from extensive brain edema after stroke or trauma. The activity of these agents against brain tumor-related edema has not been examined systematically. These drugs lead to osmotic diuresis which may cause severe shifts in electrolyte levels. Furthermore, the "rebound phenomenon", that is, edema recurrence upon treatment cessation, is a major limiting factor of their use. In a preclinical study, hypertonic saline given as a continuous intravenous infusion reduced the peritumoral edema in a rat brain tumor model [69]. However, because of the disrupted blood-brain barrier in many brain tumors, it must be considered that osmotherapeutics such as mannitol may leak into the brain parenchyma resulting in a further aggravation of the osmotic gradient [70]. Similarly, there are no data supporting a role for diuretics, e.g. furosemide, in the treatment of peritumoral edema. The use of osmotic agents should therefore be restricted to severely ill patients requiring immediate anti-edematous effects for a short period of time, e.g. during or after surgery. When steroids need to be avoided and this approach is considered clinically appropriate, e.g. in in patients with suspicion of lymphoma, osmotic agents may help to decrease edema-derived mass effect preoperatively until a tissue specimen has been obtained for histopathological assessment.

A small retrospective study analyzed the putative anti-edematous effects of angiotensin-II inhibitors in patients with newly diagnosed glioblastoma. It was reported that patients receiving angiotensin-II inhibitors, but not other antihypertensive drugs, required significantly

lower doses of steroids during radiotherapy [71]. This observation may be worth being pursued within a prospective trial. Other experimental treatments directed against peritumoral edema have only been assessed in preclinical studies: argatroban, a thrombin antagonist, reduced the peritumoral edema in a rodent glioma model [72]. Glyburide, a well-known antidiabetic drug, inhibits the sulfonylurea receptor 1 and reduced cerebral metastasis-related edema in rats [73]. Furthermore, caloric restriction attenuated the tumor-surrounding edema in glioma-bearing mice [74]. Whether any of these approaches will ever be assessed within clinical trials, needs to be awaited.

Expert commentary

Reducing the clinical burden derived from edema-mediated mass effect is an important task in patients with primary and secondary brain tumors. Glucocorticoids are the most frequently used agents against tumor-surrounding edema. They provide rapid albeit transient relief from clinical symptoms due to edema-mediated elevated intracranial pressure. Owing to their significant side effects, tapering should be considered whenever regarded clinically feasible. Even after several decades of research, convincing strategies that may allow for a significant reduction of steroids are lacking. An improved understanding of the underlying molecular mechanisms involved in the formation of peritumoral edema may help to develop novel therapeutic approaches. Inhibition of VEGF which may be the major player in the development of edemas in brain cancers results frequently in a considerable anti-edema effect. However, anti-VEGF therapies are expensive and far away from representing convincing alternatives to steroids. Boswellic acids, in contrast, have a more favourable price level and bear mostly only minor side effects. Based on the results of smaller patient series and a more recent larger trial, it may be concluded that they have a certain steroid-sparing effect. Therefore, it might be warranted to assess boswellic acids and their anti-edema efficacy in larger studies.

Five-year view

Alternatives which may help to reduce the long-term administration of steroids are urgently needed in order to avoid their manifold side effects. Based on data published by Recht et al.

[50], corticorelin acetate may currently be the most promising agent in this regard. However, several issues need further clarification such as the potential beneficial effects of the compound in patients who require rather small steroid doses. Whether corticorelin acetate in these patients may allow for a complete abstinence from steroids has not yet been examined. Furthermore, long-term toxicity as well as some safety issues, e.g. the combination with other compounds, is largely unknown. It remains to be seen whether the drug will be approved within the next years based on the available data. Further advances may arise from the ongoing research on H15 and similar *boswellia serrata* extracts. As with all other agents which have only been assessed within small series for their potential anti-edema activity, neurooncologists must strive for prospective, randomized-controlled trials in order to delineate their clinical use. Currently, no specific anti-edematous treatment based on the histology of the underlying tumor is available. A better understanding of the molecular mechanisms causing edema in different histological tumor entities may help to develop novel therapeutic strategies targeting edema.

Key issues

- Peritumoral edema can occur in virtually all CNS neoplasms and is most common in high-grade gliomas and metastases
- Several factors contribute to the development of vasogenic edema including the secretion of VEGF by tumor cells
- The mass effect derived from tumor-associated edema increases intracranial pressure and results in neurological symptoms, significantly contributing to morbidity
- Steroids are the mainstay of anti-edematous therapy. Their administration frequently leads to clinical improvement and symptom relief
- The mid- and long-term use of steroids is limited due to their numerous side effects such as metabolic changes, osteoporosis, myopathy, increased risk for opportunistic infections, psychiatric alterations and many more
- Corticorelin acetate, a synthetic analog of corticotropin releasing factor, may help to reduce steroids doses and steroid-related side effects
- Anti-angiogenic agents such as the VEGF inhibitor bevacizumab have pronounced anti-edema effects in many brain tumor patients

- Several agents with putative anti-edematous activity have only been assessed in preclinical models or small patients series including COX-2 and angiotensin-II inhibitors and further clinical testing is required

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