Chapter 7
Central Nervous System

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Abstract Tumors of the central nervous system (CNS) differ in many ways from other tumors. First, these tumors are separated by an important natural barrier, the blood–brain barrier, with the aim of defending the CNS from external noxa but, in the case of cancer, limiting the efficacy of therapy. Second, the tumors of the CNS are malignant not only because of their biological behavior but because of their localization. Even very small and slow-growing tumors localized at important regions of the brain, like the brainstem, can have serious, deleterious, and fatal impact. Finally, tumors of the CNS have a very important impact on the quality of life of patients, with long-term disabling effects on everyday

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life. Therefore, tumors of the CNS require early diagnosis and a rapid multidisciplinary approach to choose optimal treatment. In these cases, special attention must be taken to select chemotherapies and targeting agents that do cross the blood–brain barrier.

The focus of this chapter is side effects from chemotherapies used to treat a wide variety of tumors, from gliomas to metastatic (meningeal disease) lesions from other organs. This chapter will discuss the main complications from the treatment of CNS disease (glioma, medulloblastoma, and carcinomatous meningitis), specifically from radiotherapy, from cytotoxic and targeted anticancer therapy, and from supportive care measures.

Keywords CNS • glioblastoma • Temozolomide • Bevacizumab Intrathechal chemotherapy • Blood–brain barrier

Introduction

The focus of this chapter is on side effects of treatment of primary tumors of the central nervous system (CNS) and particularities of supportive care with tumor manifestations in the CNS. For the management of secondary (metastatic) tumor manifestations in the CNS, the reader should also refer to the respective chapters of the primary tumor of origin. As a general rule, brain metastases will respond in a similar manner to chemotherapy than other systemic disease, provided the agent crosses the blood–brain barrier and sufficient drug concentrations in the CNS can be achieved. This chapter will briefly discuss the main complications from the treatment of CNS disease, specifically for radiotherapy, from cytotoxic and targeted anticancer therapy, and from supportive care measures.

Classification of primary brain tumors according to the World Health Organization is based on their cell of origin. The most common malignant tumors in adults are glioma, which account for approximately 2 % of all cancers; in children and young adults, embryonic tumors in the CNS are among the

Table 7.1 The most commonly used agents in CNS tumors

Temozolomide
Nitrosoureas
Carmustine (BCNU)
Lomustine (CCNU)
Fotemustine
Nimustine (ACNU)
Procarbazine
Vincristine
Bevacizumab
Irinotecan (CPT11)
Ifosfamide
Carboplatin
Etoposide
Cytarabine
Methotrexate
Thiotepa

most frequent tumor manifestations. Primary CNS lymphoma is often (but not exclusively) associated with chronic immunodeficiency (e.g., AIDS, after organ transplant).

Due to their infiltrative nature and their localization in the CNS, a complete resection of gliomas and other brain tumors is often not achievable. Even after macroscopic gross total resection, gliomas virtually always recur. Thus, additional therapy with radiation and/or chemotherapy is indicated. The blood–brain barrier, although often partially disrupted at the site of the tumor, is an obstacle to delivery of adequate concentrations of chemotherapy to the brain. The most commonly used agents in the treatment of primary CNS tumors are summarized in Table 7.1.

Radiotherapy

Historically, radiotherapy has been the sole treatment of malignancies in the brain. The radiation fields, the dose, and the fractionation vary from precise stereotaxic irradiation (radiosurgery) to focal or whole brain radiotherapy. The primary determinants of toxicity are the administered cumulative dose, the dose of individual fractions, and the irradiated volume. Vulnerability and radiosensitivity differ between the various structures of the CNS. In high-grade glioma, focal radiotherapy to the tumor with a safety margin of 1.5–2 cm up to a total dose of approximately 60 Gy in 1.8- to 2-Gy fractions is commonly delivered. At doses above 60 Gy, the risk of long-term damage to the normal brain tissue increases exponentially, with no increase in efficacy. For low-grade glioma doses of 50 Gy suffice. For brain metastases with overall poor prognosis, a simpler hypofractionated regime of 10 × 3 Gy is frequently prescribed. The main side effects can be divided into reversible short-term and irreversible long-term toxicity (Table 7.2). Acute side effects are hair loss (may persist), fatigue, somnolence, and nausea and vomiting. Since radiotherapy induces inflammation, the tumor- and mass effect-related symptoms like headaches, nausea and vomiting, and neurologic symptoms may temporarily increase during radiotherapy. The practice of routine prophylactic steroid administration during cranial irradiation has been abandoned, and steroids should be introduced in case of symptoms only. The major long-term side effect of irradiation of the brain is leukoencephalopathy, which is due to destruction of the myelin sheaths covering nerve fibers. The symptoms are greatly variable, from a frequent pure radiologic finding without clinical symptoms to mild confusion and cognitive impairment to progressive invalidating dementia and functional deficits. Factors that contribute to the development of neurocognitive deficiency include volume of irradiation, patient's age (brains of older patients are more vulnerable), tumor volume and localization, and genetic factors [1]. Because of the developing brain, children below the age of 3 years are particularly sensitive to radiotherapy. In adults, 26 % of patients develop leukoencephalopathy as early as 3 months after the

Table 7.2 Side effects of radiotherapy after brain or spinal cord irradiation

Time after irradiation	Symptoms
Brain	
Acute (days)	Increased ICP, nausea and vomiting
Early delayed (weeks)	Somnolence syndrome, fatigue, hair loss, symptoms of tumor recurrence
Delayed (months–years)	
(a) Necrosis	Dementia, symptoms of tumor recurrence
(b) Leukoencephalopathy	Dementia or asymptomatic
Spinal cord	
Early delayed (weeks)	Lhermitte's sign
Delayed (months–years)	
(a) Necrosis	Transverse myelopathy
(b) Hemorrhage	Acute myelopathy
(c) Motor neuron disease	Flaccid paraparesis, amyotrophy
(d) Arachnoiditis	Asymptomatic
(e) SMART syndrome	SMART syndrome: stroke-like migraine attacks after radiation therapy

end of whole brain radiotherapy. After 3 months of whole brain radiotherapy. Preexisting leukoaraiosis seems to be a major determinant of long-term damage [2].

Chemotherapy

Drug therapy is used alone, as single agents, or in combination regimens and concomitant with radiotherapy. In the following sections, the most commonly used agents are discussed, with specific focus on dosing and toxicity when used for the treatment of brain tumors and CNS disease.

Agents Commonly Used Against Glioma

Temozolomide (EU, Temodal; USA, Temodar)

Temozolomide (TMZ), an alkylating cytotoxic agent, is nowadays the most commonly used drug in the treatment of malignant glioma [3]. It is used in a variety of different dosages and regimens, usually either as a single agent or in combination with concomitant radiotherapy (Table 7.3 and Fig. 7.1) [9]. Since it is rapidly absorbed in the gut with almost 100 % bioavailability, oral formulation is possible and permits ease of administration and dosing. It readily crosses the blood–brain barrier, allowing for cytotoxic tumor tissue concentrations [10].

TMZ is usually well tolerated. Gastrointestinal intolerance is the most common side effect, while myelosuppression is dose limiting. The severity of the observed toxicities is variable, and the incidence depends on the dosing regimen. For the scheme of intermittent, once a day for 5 consecutive days administration, antiemetic prophylaxis is almost always required. Continuous low-dose and metronomic regimens often do not require any antiemetic drug beyond the first 2–3 days of administration. Profound lymphocytopenia, on the other hand, is commonly observed with continuous dosing, while late thrombocytopenia is more frequent with the intermittent regimen.

Table 7.4 presents the common side effects of TMZ, all grades, compared to radiotherapy.

Hematologic

Myelosuppression, in particular late occurrence (>21 days after treatment start) thrombocytopenia, is a side effect of TMZ.

During chemoradiotherapy, TMZ is given at a daily (7/7d) dose of 75 mg/m^2, approximately, 1–2 h before irradiation (including weekends and days without radiotherapy), starting simultaneously with the first day of radiotherapy until the last day of irradiation, which is usually 30 fractions over 40–49 days max [5]. Although myelosuppression is rarely observed before

TABLE 7.3 Dosing regimens of TMZ

Schedule	Dose (mg/m²)	Dose intensity (mg/m²/week)	References
Daily for 5 days, repeat every 28 days	150–200	250	Initially an approved standard dosing
Daily for 42–49 days	75	315	Brock et al. [4] approved in conjunction with radiotherapy (Stupp et al. [5])
Daily continuously nonstop (metronomic)	50	350	Perry et al. [6]
Daily for 7 days, repeat every 14 days	100–150	525	Tolcher et al. [7]
Daily for 21 days, every 28 days	75–100	525	Tolcher et al. [7]
Daily for 3 days, every 14 days	300	450	Vera et al. [8]

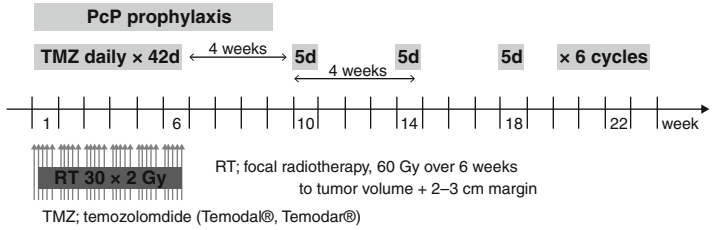

FIGURE 7.1 Standard-of-care radiochemotherapy regimen. *TMZ* temozolomide (Temodal®, Temodar®)

week 3, complete blood counts are to be performed weekly. Low blood counts may occur several weeks after the end of chemoradiotherapy (continue to monitor CBC!). When the platelet count drops below 75×10^9/L (grade 2) or the neutrophil count is $<1 \times 10^9$/L (grade 3), chemotherapy should be temporarily suspended. It can be restarted once the values have recovered (neutrophils > 1.5, thrombocytes > 100, or toxicity grade < 2). Occurrence of toxicity during concomitant chemoradiotherapy is not a reason for not proceeding with standard adjuvant/maintenance chemotherapy after the end of the chemoradiotherapy.

With the standard 5-day, daily dosing regimen, the nadir commonly occurs after 3 weeks (days 21–28). During initial treatment cycles, blood counts should be checked on day 22 and day 29 (= day 1 of the subsequent cycle). Occasionally, patients require an additional delay of 3–14 days until blood counts recover. In case of severe myelosuppression (e.g., ≥ grade 3 or delayed recovery), dose reduction by 50 mg/m^2 is recommended. In case of hematologic toxicity during chemoradiotherapy, prudence is advised when dosing the initial cycle of subsequent adjuvant therapy (dose for cycle 1: 150 mg/m^2/day for 5 days, to be escalated in the absence of significant hematologic toxicity to 200 mg/m^2).

Profound lymphocytopenia occurs frequently with the continuous TMZ regimen (e.g., during concomitant chemoradiotherapy) and may be further enhanced by the frequent administration of corticosteroids. These patients are at risk for *Pneumocystis jirovecii* pneumonia (PCP, formerly known as *Pneumocystis carinii*), and primary prophylaxis should be

Table 7.4 Common side effects of temozolomide (TMZ), all grades, compared to radiotherapy (RT) only

	RT alone (%)	RT + TMZ (%)	Comment/treatment/ prevention
Nausea	16	36	5-HT3 agonist, domperidone, or metoclopramide, 30 min before TMZ. Take caps on an empty stomach. Eat small, frequent meals
Vomiting	6	20	See above
Constipation	6	18	Laxatives; drink well; exercise, if possible
Headache	17	19	Painkillers
Fatigue	49	54	Rest
Convulsions	7	6	Optimize antiepileptic treatment. Interactions with TMZ and some antiepileptic drugs
Anorexia	9	19	
Skin rash	15	19	Avoid sun exposure, especially when undergoing RT
Alopecia	63	69	RT, not TMZ, will induce alopecia
Infection	5	9	
Leukopenia/ neutropenia	6	9	See paragraph on hematotoxicity
Thrombocytopenia	1	4	See paragraph on hematotoxicity

Table created with data from Cohen et al. [11] and [5]

considered (Table 7.5). Other complications associated with an immunosuppressed state are reactivation of herpes zoster infection, exacerbation of chronic hepatitis, and Kaposi sarcoma.

Table 7.5 Prophylaxis of Pneumocystis pneumonia

A high frequency of opportunistic infections was observed in the first trials using the continuous low-dose TMZ regimen [12, 13], and a primary prophylaxis was introduced for subsequent clinical trials. The manufacturer's recommendation is primary prophylaxis during TMZ/RT (see Temodal/Temodar package insert). Alternatively, some institutions follow on a regular basis the total lymphocyte and CD4-positive lymphocyte count, and prophylaxis is proposed if the CD4 value is less than 200–250/mm^3 or the total lymphocyte count is <500 mm^3. Commonly recommended prophylactic regimens are as follows:

Agent	**Dose and frequency**	**Remarks**
Pentacarinat (pentamidine)	300-mg inhalation, every 4 weeks	In the authors' experience the preferred regimen
Trimethoprim-sulfamethoxazole (Bactrim, Septra)	1 double-strength (160/800 mg) tablet 3×/week (Monday, Wednesday, Friday)	Cave myelosuppression with sulfa drugs
Dapsone (Dapsone)	100 mg 1×/day	If intolerance to TMP-SMX

Gastrointestinal

One of the most common side effects of TMZ is mild to moderate nausea and occasional vomiting that can be prevented by a low-dose prophylactic administration of 5-HT3 inhibitors (e.g., lower-dose ondansetron, 4 mg; granisetron, 1 mg) or metoclopramide in almost all patients. Because 5-HT3 antagonists are associated with their own toxicity, like constipation and headache, chronic repeated dosing is to be avoided. In the authors' experience, a low dosage of the 5-HT3 antagonist during the first 2–5 days of a cycle is usually sufficient. With the continuous TMZ dosing regimens, a simple antiemetic prophylaxis with metoclopramide or domperidone will commonly

suffice, and up to half of the patients may not need any antiemetic treatment beyond the first days of treatment.

Alopecia

TMZ does not induce alopecia; however, radiotherapy will. It can be partial or complete and is seen in up to 63 % of patients after radiochemotherapy.

Infection (Oral Thrush, Wound Infection, Herpes Simplex)

Immunosuppression (e.g., lymphocytopenia) induced by chronic TMZ administration (and often exacerbated by concomitant corticosteroids) will lead to oral candidemia, herpes reactivation, or wound infection. Other than consideration of PCP prophylaxis (as described earlier), prophylactic antibiotic therapy is not recommended.

Neurologic and Psychiatric

Side effects such as anxiety, sleeping disorder, emotional instability, drowsiness, dizziness, confusion, memory loss, blurred vision, and concentration difficulties have been observed. These side effects may be partly caused by TMZ, but they have also been observed in patients treated by radiotherapy only and may be explained by the tumor itself or the frequent corticosteroid administration.

Before the widespread utilization of TMZ alone and concomitant with radiotherapy, the combination of procarbazine, lomustine (CCNU), and vincristine (known as the PCV regimen) has been used since the 1980s [14]. Due to ease of administration and overall excellent tolerance, TMZ has largely replaced the PCV regimen; superiority of either treatment has never been formally investigated. The PCV regimen requires intravenous administration of vincristine, and the regimen is associated with a high incidence of myelosuppression, occasional infections, and frequent treatment delays.

Nitrosoureas (Lomustine, Carmustine, Nimustine, and Fotemustine)

Lomustine (CCNU), carmustine (BCNU), nimustine (ACNU), and fotemustine are alkylating nitrosourea anticancer cytotoxic drugs [15]. They produce DNA and RNA alkylation. They are greatly soluble in lipids, which allows their passage through the blood–brain barrier. The main toxicities are hematologic and gastrointestinal. Myelosuppression is the dose-limiting side effect. Lomustine is the drug most commonly used for glioma therapy and is one of the components of the PCV regimen (Table 7.6). ACNU and fotemustine are used occasionally in some countries such as Germany and Japan (ACNU) and France and Italy (fotemustine). Carmustine was for long the standard of care in the United States [17]. As a single agent the standard dose of lomustine is 130 mg/m^2; however, in combination and in patients having received prior chemotherapy, only a reduced dose of 90–110 mg/m^2 can be tolerated. In many countries, lomustine comes only in capsules of 40 mg, thus limiting dose titration. It is given by mouth once every 6–8 weeks.

Myelosuppression

The myelosuppression is dose dependent and cumulative and occurs late in the treatment cycle (nadir fifth week, occasionally even later). Thrombocytopenia observed around day 28 is often followed by neutropenia occurring after day 35. The leukopenia can persist up to 2–3 months after the end of the treatment.

Gastrointestinal System

Frequency of side effects is variable. Nausea and vomiting most often appears 4–6 h after administration and may persist for 24–48 h, associated with anorexia for 2–3 days. Antiemetic treatment usually has a good effect on nausea. Mild and clinically nonsignificant elevation of liver function tests is often observed. Stomatitis and diarrhea are often seen.

Table 7.6 The PCV regimen

The PCV regimen was developed in the late 1970s [16], aiming at a non-cross-resistant combination of three agents with activity against brain tumors. For vincristine, antitumor activity was assumed based on the neurologic toxicity induced by this agent. For over 20 years, this regimen was considered the most active treatment against malignant glioma and used in many large clinical trials. Unfortunately, a sufficient antitumor activity as adjuvant treatment in newly diagnosed glioma patients could never be established, albeit that antitumor activity was demonstrated in subgroup analyses. One reason for failure may have been the substantial toxicity, in particular the overlapping hematotoxicity induced by these agents, which led to frequent delays, early treatment discontinuations, or fatal complications. Several modifications and variations of the regimen exist.

Agent	**Dose (mg/m^2)**	**Days of administration**
Modified PCV		
Procarbazine	60	8–21
CCNU	110	1
Vincristine	1.4	8, 29
British PCV		
Procarbazine	100	1–10
CCNU	110	1
Vincristine	1.5	1

Neurologic System

When combining lomustine with other drugs, neurologic side effects such as apathy, confusion, stuttering, and disorientation have, in rare cases, been described.

Respiratory System

One of the limitations of nitrosourea therapy is idiopathic pulmonary fibrosis, most commonly seen with carmustine. Moderate to severe respiratory insufficiency is thus a relative contraindication to the treatment with nitrosoureas. If pulmonary symptoms occur, presenting often with a diffuse infiltrate,

and once other causes have been ruled out, treatment is a prolonged course of corticosteroids [18].

Procarbazine

Procarbazine is another alkylating agent causing DNA cross-links followed by DNA breaks. Myelosuppression is the main side effect, with neutropenia and thrombocytopenia being dose limiting. Nausea and vomiting are common. Within the PCV regimen, the dosage is 60 mg/m^2 daily PO for 14 days (day 8–day 21); as a single agent, doses of 100–150 mg/m^2 for 14 days are usually well tolerated. Procarbazine comes as capsules of 50 mg each.

Hematologic

Toxicity (neutropenia, thrombocytopenia) may commence 1 week after the beginning of the treatment, and it can persist up to 2 weeks after withdrawal.

Gastrointestinal

Nausea and vomiting can usually be prevented by standard antiemetic treatment.

Immunologic and Skin Rash

Hypersensitivity reactions with eosinophilia and fever are common. The reactions can be IgE-mediated but are also associated with a type III reaction manifested by pulmonary toxicity and cutaneous reactions [19]. The higher frequency of hypersensitivity reactions in brain tumor patients has been associated with the concomitant administration of antiepileptic drugs [20]. A diffuse, pruritic, erythematous maculopapular rash has been reported in 12–35 % of glioma patients. Note that procarbazine inhibits alcohol dehydrogenase and may cause disulfiram-like reactions when a patient consumes alcohol.

Neurologic

Drowsiness and peripheral neuropathy are regularly seen.

Respiratory

Rare cases of pneumonitis (see immunologic) have been reported; it may be severe and irreversible. The treatment is procarbazine withdrawal and corticosteroid therapy [21].

Hypertensive Crisis

Food containing high levels of tyramine (e.g., red wine, overripe bananas, mature cheese) may cause hypertensive crisis, since procarbazine is a monoamine oxidase (MAO) inhibitor.

Vincristine

Vincristine is a vinca alkaloid that binds to tubulin dimers, inhibiting microtubule assembly and in turn blocking cell division during the mitotic phase [22]. The side effects of vincristine are dependent on the total dose given. The dose-limiting side effect is neurotoxicity. Recent studies have questioned whether vincristine sufficiently penetrates through the blood–brain barrier, and it may not be an effective agent against brain tumors [23]. The standard weekly dose is 1.4 mg/m^2 (usually capped at a maximum dose of 2 mg), as part of the PCV regimen given on days 8 and 29.

The most common side effect is alopecia, while the most troublesome is neuromuscular adverse reactions. Leukopenia and severe myelosuppression are rare. Vincristine is metabolized in the liver via the CYP3A4-mediated enzymes; it may thus increase metabolism of CYP3A4-dependent antiepileptic drugs. Caution is advised in patients with hepatic insufficiency.

Alopecia

This is the most common side effect. Regrowth of hair usually happens 6 weeks after the interruption of treatment.

Neuromuscular

Frequently, a sequence in the development of the neuromuscular side effects can be observed with the treatment continuation. The initial sensory impairment and paresthesia are followed by

neuropathic pain, and finally motor difficulties occur. No treatment that could reverse the neuromuscular manifestations has so far been reported.

Gastrointestinal

Constipation with or without pain has been regularly seen; therefore, prophylactic laxatives should be proposed. Rarely, paralytic ileus can be seen, especially in young and elderly patients, which upon withdrawal of vincristine can regress spontaneously.

Ocular

Rarely, visual side effects such as transient cortical blindness, optic nerve atrophy with blindness, and nystagmus can occur.

Neurotoxicity

Inadvertent intrathecal administration of vincristine can cause ascending radiculomyeloencephalopathy, which in most cases is fatal. Immediate cerebrospinal fluid aspiration must be followed by intrathecal irrigation, including intrathecal administration of fresh-frozen plasma that can eventually bind vincristine. A few cases of patients who received rapid supportive care and survived intrathecal vincristine have been reported [24–26].

Pulmonary

In rare cases administration of vincristine has led to bronchospasm, especially when combined with mitomycin C. This can occur immediately after the administration or several hours later. In these cases vincristine should not be readministered.

Accidental Extravasation

It can cause severe local reaction and tissue necrosis. Hyaluronidase injection at the site of extravasation must be considered, since vincristine breaks down hyaluronic acid in the connective/soft tissue, allowing the further dispersion of

vincristine. Heat packs applied for 20 min QID during 3 days are recommended because this can lead to vasodilatation and consequently to diffusion and elimination of the drug from the site of injection [27].

Bevacizumab (Avastin)

Bevacizumab is a monoclonal neutralizing antibody inhibiting the growth factor VEGF-A, the ligand to the VEGF receptor, highly expressed on tumor-associated endothelial cells [28]. This is an attractive treatment target in patients with glioblastoma because this tumor is highly vascular and expresses high levels of VEGF-A. The commonly used dose of bevacizumab is 10 mg/kg every 2 weeks, although lower doses might be equally effective. Formal dose-finding studies in brain tumors were not conducted. Bevacizumab is approved in recurrent/relapsed glioblastoma in the United States and Switzerland. In many European countries, it is used regularly, although the extension of the indication to brain tumors was rejected by the European Medicines Agency due to the absence of any controlled efficacy data. Definitive phase III trials are finally ongoing.

While bevacizumab clearly allows the reduction of corticosteroid therapy and will lead to temporary neurologic improvement, particularly in patients with severe peritumoral edema, its effect on survival is less evident and contested. The possible modest benefit of bevacizumab has to be balanced against potential risks and toxicity and, ultimately, cost [29].

The most common side effects are hypertension, asthenia, fatigue, vomiting, diarrhea, and abdominal pain, while the most serious side effects are gastrointestinal perforation, hemorrhage, and both arterial and venous thromboembolic events. There is no myelosuppression when used as a single agent.

It should be noted that administration of bevacizumab leads to a reduction in contrast enhancement, the standard metric of objective response, making the radiologic follow-up difficult. Contrast-enhanced magnetic resonance imaging has revealed a significant reduction of the vascular supply, as evidenced

by a decrease in intratumoral blood flow and volume. The vascular remodeling induced by anti-VEGF-A treatment leads to a more hypoxic tumor microenvironment. Concerns have been raised that the tumor's remodeling may lead to a more aggressive tumor phenotype. A metabolic change in the tumor cells toward glycolysis leads to enhanced tumor cell invasion of the normal brain tissue [30, 31].

Hypertension

Bevacizumab is thought to induce hypertension by decreasing nitric oxide production, resulting in vasoconstriction [32]. This also leads to increased sodium reabsorption in the kidney. Hypertension is a dose-dependent side effect; the frequency increases exponentially with increased doses [33]. With the commonly used high doses of bevacizumab (10 mg/kg), hypertension of any degree has been observed in up to one-third of the patients; however, it was considered severe (≥ grade 3, i.e., systolic blood pressure >180 mmHg and diastolic blood pressure >110 mmHg) in only 5 % [34]. Preexisting hypertension should be treated before initiation of bevacizumab. Hypertensive exacerbation will further increase the risk for intracranial hemorrhage.

Figure 7.2 shows the management of hypertension and proteinuria. The management of bevacizumab-induced hypertension follows the general principles of hypertension treatment [35]. In patients with cardiovascular risk factors, the treatment goal is 130/80; in others, 140/90. The antiangiogenic treatment should be withdrawn if clinically significant hypertension persists despite proper management or in case of a hypertensive crisis or symptomatic hypertensive encephalopathy (headaches, attention disorder, confusion, or coma).

Patients with previous hypertension are, like all hypertensive patients, at higher risk of developing proteinuria. A potential mechanism for proteinuria is by the inhibition of VEGF on the podocytes leading to renal damage [36]. Urinary dipstick analysis should be performed before initiating and during the treatment.

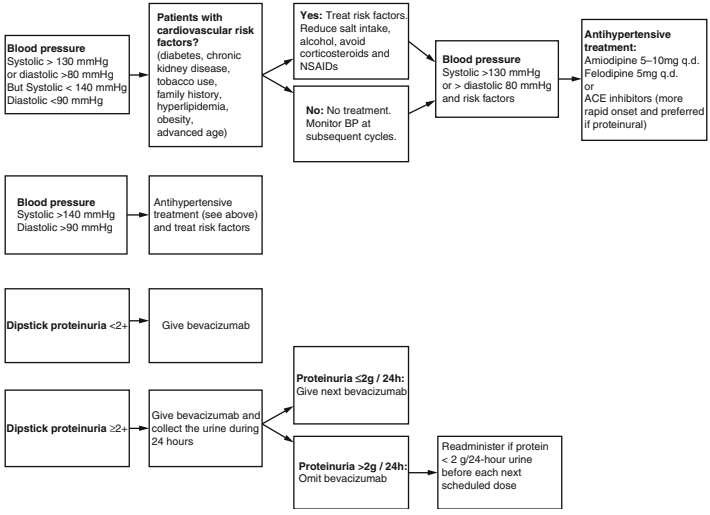

FIGURE 7.2 Management of hypertension and proteinuria

As long as proteinuria over 24 h is not less than 2 g, bevacizumab should not be given. Nephrotic syndrome occurs in 0.5 % of patients, and treatment must be withdrawn. Proteinuria is seen less commonly in patients with CNS tumors than in other cancer types, likely explained by the shorter exposure to bevacizumab due to tumor progression occurring at a median of 4 months. Similar to patients with hypertension and proteinuria, agents such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are the first choice.

Arterial and Venous Thromboembolism

Patients with gliomas are at higher risk of venous thrombotic events [37], while the incidence of arterial thromboembolism is not known to be increased. Patients treated with bevacizumab are at higher risk of developing arterial and/or venous thromboembolism [38]. This includes stroke,

transient ischemic attacks, myocardial infarction, deep venous thrombosis, and pulmonary embolism. Patients with a previous history of arterial thromboembolism or age older than 65 are at higher risk of developing thromboembolic complications and must be carefully monitored. Bevacizumab therapy should be definitively discontinued in patients having presented with an arterial thrombotic event. The presence of a venous thromboembolic event is a relative contraindication to continuation of bevacizumab therapy; risks and benefits need to be evaluated individually. The requirement of systemic anticoagulation may slightly increase the risk for an intracranial hemorrhage, a risk that is already more pronounced owing to the presence of recurrent tumor in the brain (high vascularization of recurrent glioblastoma may lead to spontaneous bleeding) and further exacerbated by bevacizumab therapy. Nevertheless, current, albeit limited, experience indicates no substantial increase of serious intracranial hemorrhage when patients are treated simultaneously by systemic anticoagulation and bevacizumab [39]. Low molecular weight heparins (LMWH) are more often used than oral anticoagulants, since fewer drug interactions are expected with potentially improved efficacy [40].

Bleeding

Patients treated with bevacizumab have an increased risk of bleeding, especially at the tumor site [41]. Higher doses of bevacizumab increase the risk of bleeding. The mechanism of the bleeding is thought to be via inhibition of the endothelial cell survival and proliferation leading to damaged blood vessels. The most common type of bleeding is epistaxis, but more serious bleeding like intracerebral, gastrointestinal, or pulmonary can also be seen. If any grade 3 or 4 bleeding occurs, the treatment must be withdrawn. The risk of intracranial hemorrhage does not seem to be more elevated in patients with glioblastoma than in other patients treated with bevacizumab. Intracranial bleeding more frequently occurs during progression, regardless of bevacizumab use.

Surgical Complications After Prior Bevacizumab Therapy

Wound Healing

Antiangiogenic therapy interferes with wound healing [42]. Vascular endothelial growth factor is essential for neovascularization, and bevacizumab interferes with this mechanism. The long biological half-life of bevacizumab (median, 20 days; range, 11–50 days) has led to the recommendation not to administer bevacizumab 4 weeks before and 4 weeks after undergoing major surgery or before complete healing of the wound. One study showed that bevacizumab interferes more with wound healing if it is given preoperatively than postoperatively [43].

Gastrointestinal Perforation

In a large meta-analysis with 12, 294 patients, perforation was seen in 1 % of patients [44]. Most relevant risk factors in brain tumor patients are constipation, diverticular disease, peptic ulcers, and concomitant use of corticosteroids. In any case of gastrointestinal perforation, the treatment must be immediately withdrawn.

Heart Failure

In clinical trials, congestive heart failure has been seen in patients receiving bevacizumab. The symptoms are from asymptomatic reduction of left ventricle ejection fraction on cardiac ultrasound to symptomatic heart failure needing inpatient care. Many of these studies included breast cancer patients after prior exposure to anthracyclines and/or trastuzumab. One study suggests that the toxicity may be spontaneously reversible [45].

Perfusion Reactions

Patients may develop hypersensitivity and infusion reactions. This is seen in less than 5 % of patients. The majority of reactions are mild to moderate. More severe reactions were noted

in 0.2 % of patients. Premedication is not warranted. If a reaction occurs, the infusion shall be stopped and symptoms treated. Rechallenging patients can be discussed, but it must be based on the goals of the therapy and the severity of the reaction.

Posterior Reversible Encephalopathy Syndrome

One of the infrequent but very serious side effects is posterior reversible leukoencephalopathy (PRLE) [46]. The differential diagnosis between PRLE and hypertensive encephalopathy can be difficult. The main symptoms are headache, seizures, altered mental status, nausea, troubled vision, or cortical blindness; most patients are markedly hypertensive. At CT/MR imaging the brain typically demonstrates focal regions of symmetric hemispheric edema. It is thought that the causes of PRLE can be failure of cerebral vasomotor autoregulation due to hypertension or primary endothelial damage. The mechanisms resemble preeclampsia. The symptoms usually resolve with efficient treatment of hypertension and with withdrawal of bevacizumab.

Irinotecan (CPT11)

Irinotecan is a semisynthetic derivative of camptothecin, which acts as a DNA topoisomerase I inhibitor [47]. It easily crosses the blood–brain barrier. Topoisomerase I is localized in the cell nucleus and regulates DNA topology, facilitating nuclear processes such as DNA replication, recombination, and repair. The active metabolite of irinotecan, SN-38, binds to the topoisomerase I-DNA complex. Topoisomerase I and II activities are significantly increased in malignant tumors due to DNA damage, thus making irinotecan an interesting drug for the treatment of gliomas. Irinotecan and its metabolites are secreted via the liver and depend on the P450 enzyme complex [48]. As brain tumor patients commonly receive antiepileptic drugs, drug-drug interactions may occur. Notable are phenytoin, carbamazepine and derived substances, and the nowadays rarely used phenobarbital, which

will induce cytochrome P450 CYP3A4 enzymes, leading to faster clearance of irinotecan and thus diminishing or eliminating its activity [49].

Different dosing regimens of irinotecan have been established, initially for gastrointestinal cancer [50]. In brain tumors, irinotecan has been given as a weekly ×4 administration every 6 weeks at a dose of 125 mg/m^2 or in combination with bevacizumab every 2 weeks at a 125-mg/m^2 dose. In our experience we commonly increase the dose up to 180 mg/m^2, similar to the established gastrointestinal dose. Higher doses of up to 340 mg/m^2 have been suggested for patients taking enzyme-inducing antiepileptic drugs; however, it is much safer to switch patients to the well-established non-enzyme-inducing antiepileptic agents [51].

The main side effects of irinotecan are diarrhea and hematotoxicity.

Gastrointestinal

Profound and delayed diarrhea is the dose-limiting toxicity of irinotecan. Diarrhea will occur in the majority of patients, being severe in up to 20 %. Diarrhea typically occurs in two phases: early, within the first 24 h, and late, after 5–7 days. Early diarrhea is due to the cholinergic toxic syndrome (see later section) and self-limiting. Patients having received radiotherapy on the pelvic region, patients with leukocytosis, performance status of two or more, and women are at a higher risk of developing diarrhea. Late diarrhea occurs several days after irinotecan administration. Most common is the appearance of diarrhea on the fifth day in the case of a schedule of every 2 weeks (high dosage) and on the eleventh day in case of the weekly treatment. Patients must be informed of this side effect; in case of diarrhea adequate oral rehydration is imperative. Loperamide, 4 mg as an initial dose and 2 mg with every loose stool, shall be given at the first signs of diarrhea, up to eight or more doses/24 h. Repeated loperamide administration every 2 h is recommended for another 12 h after the last episode of diarrhea, but total exposure should not exceed 48 h, thus avoiding consecutive paralytic ileus.

Delayed diarrhea often coincides with myelosuppression; thus, patients at this stage are particularly vulnerable. Forced rehydration, if needed intravenous, should be considered, with low threshold to hospitalization in case of prolonged diarrhea, dehydration, or fever.

In patients with hyperbilirubinemia (1.5–3 times higher than the normal level), liver function tests must be surveyed weekly. Irinotecan is to be withdrawn if bilirubin is three times higher than normal. Prophylactic antiemetic drugs are to be given before each cycle to avoid nausea and vomiting, which are a common side effects.

Hematologic

Neutropenia has been seen in almost 80 % of patients treated by irinotecan monotherapy; severe neutropenia ($<0.5 \times 10^6$ G/L) has been seen in 22 % of patients. The hematotoxicity is reversible, with a nadir around the eighth day and subsequent rapid recovery. The neutropenia is not cumulative. Anemia is seen in 58 % of patients. Thrombocytopenia is seen less frequently; approximately 10 % of patients will be seen with thrombocytes less than 100×10^6 G/L.

Dermatologic

Reversible alopecia is very common.

The Cholinergic Toxic Syndrome

This syndrome is specific to irinotecan and can be seen in up to 42 % of patients treated with irinotecan; it can be severe in one-fourth of patients [52]. The main symptoms are diarrhea, abdominal pain, hypotension, shivering, dizziness, blurred vision, miosis, transpiration, and hypersalivation while receiving the chemotherapy or within the following 24 h. The symptoms can be relieved by premedication with 0.25–0.5 mg of atropine given subcutaneously.

Other Commonly Used Agents in CNS Malignancies

For the treatment of germ cell tumors, primitive neuroectodermal tumors (PNET), and medulloblastoma, combination regimens including ifosfamide, cisplatin or carboplatin, and etoposide are frequently administered [53, 54]. The backbone of treatment of primary CNS lymphoma is high-dose methotrexate, either alone or in combination with cytarabine or ifosfamide (± the monoclonal antibody rituximab) [55, 56]. We briefly discuss ifosfamide; cytarabine and methotrexate are reviewed in the section on leptomeningeal disease. For the other agents the reader should refer to other sections of this book.

Ifosfamide

Ifosfamide is a nitrogen mustard alkylating agent and an analogue of cyclophosphamide. First, ifosfamide is activated to 4-hydroxyifosfamide in the liver, which is then transformed into the active compound isoaldophosphamide. In addition to myelosuppression, characteristic toxicities of this agent include hemorrhagic cystitis, renal insufficiency, and ill-defined diffuse cognitive and cerebellar symptoms. Common dosing is 750–1,000 mg/m^2/day as a continuous several-hour infusion for 4–5 days. The usual dose for medulloblastoma is 900 mg/m^2/day in a continuous infusion over 5 days [57].

Gastrointestinal

Nausea and vomiting is seen in approximately half of patients. Usual antiemetic prophylaxis by 5-HT3 antagonists is recommended.

Dermatologic

Reversible alopecia is very common.

Neurologic

Ten to twenty percent of patients will have symptoms of encephalopathy such as hallucinations, drowsiness, confusion, and depressive psychosis. Drowsiness is the most common symptom, and it can rapidly progress to coma. These symptoms are seen from a couple of hours to up to a couple of days after the administration of the drug. In any case, the drug should be immediately suspended. After halting the administration, the median duration of the symptoms is 3 days. Interactions with other CNS-depressing drugs must be considered and the drugs withdrawn. High doses of ifosfamide illogical truncation administered over a short time, preexisting neurologic or renal dysfunction, and low serum albumin appear to be significant risk factors. In patients with grade 3–4 encephalopathy, IV administration of methylene blue (50 mg every 4 h until symptoms resolve) may be considered. The pathophysiology of this encephalopathy is poorly understood, but the cause seems to be due to chloroacetaldehyde accumulation in the nervous system. It can be (1) directly neurotoxic, (2) deplete CNS glutathione, and (3) inhibit mitochondrial oxidative phosphorylation, leading to impaired fatty acid metabolism. Methylene blue has a redox potential and restores mitochondrial respiratory chain function; it prevents transformation of chloroethylamine into chloroacetaldehyde and restores hepatic gluconeogenesis [58]. Little evidence exists for the prophylactic use of methylene blue in combination with ifosfamide.

Kidneys and Bladder

Micro- or macrohematuria is seen very commonly. It is dose dependent and can be prevented and/or alleviated by simultaneous administration of mesna. Mesna is an organosulfur compound. It is converted to an inactivated form in the blood and filtered by the kidneys, where it is reactivated. Ifosfamide and cyclophosphamide, when given in high doses, produce the metabolite acrolein, which is toxic to the bladder. Mesna binds to and inactivates acrolein, consequently reducing local side

effects in bladder. If cystitis develops during ifosfamide administration despite correct mesna dosing, the treatment should be suspended until micro- or macrohematuria disappears. During ifosfamide infusion correct hydration is important, and the bladder must be emptied on a regular basis. Tubular damage has been proposed to be the cause of renal failure seen in some patients. Mesna does not protect against renal toxicity.

Hematologic

Patients pretreated with other chemotherapy regimens or radiotherapy and with preexisting renal insufficiency are at increased risk of myelotoxicity, which can sometimes be very important. Leukopenia is seen more often than thrombocytopenia. The nadir is at 8–10 days and is usually normalized at 3–4 weeks.

Treatment of Leptomeningeal Carcinomatosis (Carcinomatous Meningitis)

Melanoma, breast and lung cancer, and hematologic and lymphoid malignancies are the most common origins of leptomeningeal dissemination [59]. Localized metastases may be treated by focal irradiation, while diffuse meningeal involvement requires intrathecal or high-dose systemic chemotherapy. Efficacy of intrathecal therapy may be limited by perturbed cerebrospinal fluid flow. Occasionally, direct intraventricular injection or access over a surgically implanted reservoir (Ommaya or Rickham) is preferred over administration by lumbar puncture, thus allowing a more homogenous distribution of the chemotherapeutic agent. The objective is to relieve and control symptoms, while often additional systemic therapy for adequate antitumor control is needed. In patients with high-risk hematologic malignancies, prophylactic intrathecal chemotherapy is often recommended [60]. Nevertheless, literature on the value of intrathecal therapy remains scarce and lacks controlled trials.

Three agents are used for intrathecal chemotherapy: cytarabine, methotrexate, and thiotepa. Adverse reactions are not uncommon. When administered intrathecally, chemical aseptic meningitis is the most common side effect seen in 20–40 % of patients and is characterized by fever, nausea and vomiting, headache, back pain radiating to the extremities, and photophobia. This can be reduced by using preservative-free diluent (saline) and preservative-free chemotherapy preparations. Late adverse events occurring more than 4–6 months after treatment, such as leukoencephalopathy with symptoms such as dementia and ataxia, must not be forgotten. The incidence is probably underestimated; it is probably higher than 20 % in patients surviving more than 4 months.

Cytarabine

Cytarabine (araC) is an antimetabolic agent that damages DNA formation during the S phase of the cell cycle. The liposomal formulation of cytarabine [...] is lipophilic and has a long half-life. Liposomal cytarabine (DepoC -> DepoCyte) is lipophilic long half-life. The liposomal formula maintains a therapeutic concentration in the CSF for 28 days, while the conventional form is entirely eliminated within 1–2 days [61]. Conventional intrathecal dose is 50 mg; with a short half-life, this should be repeated two times a week. In contrast, a liposomal formulation of cytarabine for prolonged cytotoxic exposure exists, thus requiring one administration (50 mg) every 2 weeks only. Liposomal cytarabine is approved for leptomeningeal metastases of hematologic malignancies [62].

Systemic Doses of Cytarabine

Cytarabine is the most frequently used agent against acute leukemia. For more detailed information the reader is referred to the chapter on hematologic malignancies.

Neurologic

In approximately 10 % of patients treated with high doses (≥3 g/m^2) administered intravenously every 12 h, an acute

cerebellar syndrome develops [63]. The initial symptom is somnolence. Cerebellar signs are then noted on neurologic examination, and patients may not be able to ambulate. In many patients the symptoms usually resolve after the withdrawal of cytarabine, although prolonged and persistent symptoms have been observed. There is no specific therapy other than suspending chemotherapy.

Hematologic

High doses of cytarabine will induce profound myelosuppression.

Gastrointestinal

Diarrhea, mucositis, intestinal ulceration, and ileus can be seen. The gastrointestinal side effects are often dose limiting.

Methotrexate

Methotrexate (MTX) is a folate antimetabolite, thus interfering with DNA synthesis, repair, and cellular replication. Methotrexate has been used for a wide variety of cancers (sarcomas, lymphomas, breast cancer) and also for autoimmune disorders. Methotrexate has a very good distribution in all tissues [64]. While passage through the blood–brain barrier requires administration of high systemic doses to obtain adequate drug concentrations in the central nervous system, intrathecal administration will allow the use of lower doses for the control of leptomeningeal disease with less systemic toxicity. However, drug penetration is limited to the distribution of the cerebrospinal fluid. The dose of MTX varies greatly from oral weekly 10 mg/m^2 for rheumatoid arthritis [65] to high-dose chemotherapy of ≥3 g/m^2 in primary brain lymphomas or up to 12 g/m^2 for osteosarcoma patients [66]. The commonly used dose for intrathecal administration is 12.5–15 mg/dose, which is to be repeated once or twice per week until the CSF clears and then once a week or once a month for maintenance treatment. A more intensive regimen proposed is 15 mg/day for 5 consecutive days every 2 weeks [67]; its relative efficacy has not been formally investigated.

Hematologic

Myelosuppression can be seen when administered intrathecally.

Transverse Myelopathy

An isolated spinal cord dysfunction develops rarely hours to days after the administration of MTX without compressive lesion. Patients develop back or leg pain followed by paraplegia, sensory loss, and sphincter dysfunction. The majority of patients recover, but further administration is contraindicated.

Acute Encephalopathy

Somnolence, confusion, and seizures are seen within 24 h after treatment; they usually resolve spontaneously.

Subacute Encephalopathy

After repeated injections of MTX, motor function impairments such as paraparesis/paraplegia, tetraplegia, cerebellar dysfunction, cranial nerve paralysis, and seizures can occur.

Methotrexate Administered in High Doses Intravenously

Intravenous administration of high doses (>3 g/m^2) of MTX may also be used in the treatment of meningeal disease to achieve cytotoxic doses in the CNS. The incidence and severity of acute side effects are related to dose and frequency of administration. In primary lymphoma of the central nervous system, high-dose IV MTX is the backbone of therapy. Methotrexate is also an active agent in systemic breast cancer and may allow the control of leptomeningeal disease.

Younger patients seem to better tolerate the high-dose MTX therapy, presumably due to better end-organ function and rapid elimination. Caution is to be used in patients with renal and hepatic insufficiency. The common side effects of high-dose MTX are alopecia, neutropenia, renal toxicity (more commonly in older patients), nausea, diarrhea, and stomatitis. Hepatic toxicity with transaminitis is seen.

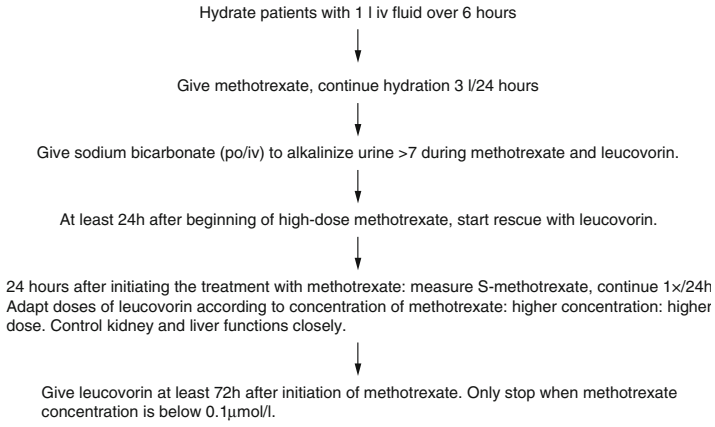

FIGURE 7.3 Administration of high-dose methotrexate with leucovorin rescue

The presence of third-space fluids is a contraindication to the administration of high-dose MTX. High concentrations of MTX can accumulate in these spaces, leading to a prolonged MTX exposure and increased toxicity. Drainage of ascites or pleural effusion must be done before introducing the drug.

The use of high-dose IV MTX has been associated with the development of chronic delayed leukoencephalopathy in patients with or without a history of craniospinal irradiation.

High-dose MTX is a potential lethal dose, and before leucovorin rescue was initiated as a standard part of the regimen, 6 % drug-related death was noted, most frequently due to the immunosuppression. Therefore, high-dose MTX administration is followed by leucovorin rescue to inhibit the toxicity of MTX on the normal cells (Fig. 7.3). The timing of the rescue is important, since introducing too early the rescue leads to a diminished effect on the tumor cells. The administration of leucovorin can be delayed up to 24–36 h without, in general, important MTX toxicity. Several schedules of leucovorin rescue exist. If the concentration of MTX is higher than 1 μmol/L at 48 h, increasing the dose of leucovorin must be considered.

The rescue must continue for at least 72 h and until the concentration of MTX is at a nontoxic level (0.01–0.1 μmol/L).

Methotrexate is principally excreted by the kidneys. A glomerular filtration rate of 60 mL/min is in general considered as a minimum for high-dose MTX administration. It should be noted that the presence of a normal serum creatinine does not predict MTX toxicity [68]. A high urine flow and an alkaline pH must be ensured to prevent precipitation of MTX in the urine, causing nephrotoxicity.

Thiotepa

Thiotepa is an alkylating agent. It crosses the blood–brain barrier well, achieving high concentrations and resulting in high levels of the active metabolite, TEPA. When administered intrathecally, thiotepa is cleared from CSF within minutes and completely eliminated within 4 h. The initial dose is 10 mg twice weekly for 4 weeks followed by one injection per week for another 4 weeks, with maintenance with one injection per month. Due to its important hematotoxicity, intrathecal administration is preferred, because it is generally well tolerated [69].

Hematologic

Systemic myelosuppression has been seen even with intrathecal administration. Systemic administration of thiotepa causes profound bone marrow suppression, especially thrombocytopenia.

Supportive Care

Corticosteroids

The use of corticosteroids is the cornerstone for symptom relief in CNS tumors [70]. Primary or secondary malignancies arising in the brain perturb the normal vasculature and induce inflammation, with water extravasation leading to an increase of the intracranial pressure (ICP). The most important symptoms

of increased ICP are fatigue, headaches, nausea and vomiting, bradycardia, and bradypnea. If untreated, increased ICP will result in brain herniation and ultimately death. The rapid initiation of corticosteroids could potentially reduce edema and also the symptoms. The most frequently used corticosteroid is dexamethasone, which has less pronounced mineralocorticoid effects than other steroids. The initial dose of dexamethasone is a 10-mg IV bolus followed by 4 mg every 6 h (16 mg/day). Since this scheme does not follow the normal diurnal changes of blood corticoids, we prefer the scheme of 8 mg twice a day in the morning and at noon. This administration reduces insomnia induced by dexamethasone. In dose-finding studies dexamethasone had been increased up to 40 mg, but there was no evidence for improved effectiveness. Once the desired acute effect has been achieved, the dose of dexamethasone should be rapidly tapered in order to avoid long-term perturbation of the hypothalamic-pituitary-adrenocortical (HPA) axis and toxicity from prolonged corticosteroid administration. Tapering consists in empiric reduction of 2–4 mg every 2–3 days. While the initial reduction in doses – empiric reduction of 2–4 mg every 2–3 days – can be rapid, the final tapering before definitive cessation of the treatment should be done more slowly, with decrements of 0.5–1 mg every 3–7 days, depending on the duration of prior steroid exposure. Common side effects are hyperglycemia, gastritis, gastrointestinal bleeding, osteoporosis, immunosuppression, skin fragility and striae, obesity, psychosis and euphoria, or myopathy with weakness of the lower extremities and neck. Steroid-induced myopathy and secondary diabetes may be misleading of disease progression and need to be excluded. Restrictive steroid prescription and appropriate surveillance may prevent these frequent complications.

Antiepileptics

The most common side effects of antiepileptic drugs (AEDs) are gastrointestinal toxicity in the form of nausea, vomiting, and diarrhea, and skin rash. Further common side effects of

AEDs are sleepiness and unsteadiness. Carbamazepine, phenobarbital, phenytoin, and sodium valproate could induce osteoporosis or osteomalacia. Furthermore, AEDs can influence memory, especially when high doses are applied. In case side effects are detected, either dose reduction should be tried or a rotation should be proposed with an AED with a different class of effect. Antiepileptic drugs such as phenytoin, phenobarbital, and carbamazepine induce the hepatic enzyme P450 (enzyme-inducing antiepileptic drugs, EIADs). Several chemotherapeutic agents, including, irinotecan, lomustine, vincristine, and procarbazine, are metabolized by the cytochrome P450. While patients with malignant gliomas are treated with these therapies, their metabolism can be increased and thus can lead to diminished efficacy. Brain tumor patients treated with EIAEDs are recommended to change to third-generation antiepileptic drugs like levetiracetam.

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