Primary Central Nervous System Lymphomas

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Abstract

Radiotherapy (RT) after systemic chemotherapy including high-dose (HD) methotrexate is widely accepted as the standard treatment for primary central nervous system lymphoma (PCNSL). Treatment must consider the blood brain barrier as it characterizes the clinical behavior of PCNSL. For consolidation RT in patients with complete remission (CR) after chemotherapy, 23.4–30 Gy of whole-brain radiotherapy (WBRT) is recommended. For salvage RT in patients with non-CR or recurrent disease (RD) after chemotherapy, 36–45 Gy of WBRT or 30 Gy of WBRT followed by 10–20 Gy of boost irradiation is recommended. The reported 5-year survival rate of PCNSL patients is 30–50%; it is worse than for patients with other extranodal lymphomas. Late neurological toxicity is a major problem in long survivors after HD methotrexate and WBRT. Chemotherapy alone may be considered in elderly PCNSL patients who are at high risk for radiation-induced neurocognitive dysfunction.

Keywords

Central nervous system lymphoma (PCNSL) • Whole-brain radiotherapy (WBRT) • Intraocular lymphoma • High-dose methotrexate • Neurocognitive dysfunction

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1.1 Introduction

Primary central nervous system lymphoma (PCNSL) accounts for around 3% of all primary brain tumors; it is more frequent in adults 60 years or older. The most common treatment for PCNSL consists of chemotherapy with high-dose methotrexate (MTX) followed by radiotherapy (RT). Although the prognosis of PCNSL patients has improved by the establishment of regimens involving high-dose MTX, their 5-year survival rate is 30–50% and worse than for patients with other extranodal lymphomas [1, 2]. RT plays an important role in the treatment of PCNSL and is used for definitive-, consolidative-, salvage-, and palliative treatment.

1.2 Pathology

Most PCNSLs are diffuse large B-cell lymphomas (DLBCLs). AIDS-related PCNSL is less frequent in Japan than in Western countries. Usually, PCNSL presents with parenchymal infiltration with extensive brain edema and potential multicentricity. Autopsy studies of PCNSL patients demonstrated tumor cell infiltration far beyond T2 hyperintensity area in magnetic resonance imagings (MRI) [3]. The highly infiltrative and multicentric nature of PCNSL warrants the use of whole-brain radiotherapy (WBRT) for consolidation irrespective of the size, number, or location of the primary tumors observed on pre-chemotherapy MRI scans [4].

1.3 Pretreatment Evaluation

Most patients with PCNSL suffer neurological symptoms or convulsions. For diagnostic workup, computed tomography (CT)/MRI studies and surgical biopsy are usually performed. To differentiate PCNSL from metastatic disease from extracranial lymphomas, FDG-PET or whole-body CT studies are useful. The pretreatment tumor size, -number, and -location should be evaluated on MRI scans shortly before the start of treatment for an exact estimation of the response. Ophthalmologic examination to detect ocular involvement should be considered regardless of visual symptoms because approximately 10–25% of patients with PCNSL develop intraocular involvement [5].

1.4 Treatment Strategy

RT after systemic chemotherapy including high-dose (HD) MTX is widely accepted as the standard treatment for PCNSL. For patients intolerant of full chemotherapy due to a poor performance status, advanced age, or previous/coincidental disease, RT alone is a treatment option with curative intent [2]. The use of MTX concurrent with or after RT may be associated with an increased

risk of leukoencephalopathy. The intrathecal administration of MTX is not recommended as clinical practice because of the potential risk of leukoencephalopathy. Chemotherapy alone has been considered as an alternative approach in elderly PCNSL patients at high risk for radiation-induced neurocognitive dysfunction. The role of surgical intervention is limited to biopsy for a histopathological diagnosis [6].

1.5 Chemotherapy

Previously, treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), the standard chemotherapy for most DLBCLs, was used to treat PCNSL. However, its effectiveness was unsatisfactory [7, 8]. Now the high efficacy of HD MTX has been widely recognized [1, 2] and its upfront use alone or in combination with other drugs, including rituximab, vincristine, and procarbazine, is recommended [9, 10]. The clinical benefit of adding temozolomide to HD MTX is under investigation [11]. The combination of systemic chemotherapy plus intraventricular chemotherapy with MTX (≥ 3.5 g/m^2), Cytarabine (Ara-C), and dexamethasone has been reported to prolong the response duration [12, 13].

1.6 Radiation Therapy (Indications)

1.6.1 Consolidation RT in Patients with CR After Chemotherapy

Consolidation RT is a traditional curative treatment option for nodal- and extranodal lymphoma patients who achieved CR after systemic chemotherapy. The omission or deferral of consolidation RT is now considered in patients with several lymphoid malignancies including PCNSL to avoid radiation-induced toxicity or a possible radiation-induced second malignancy.

Since the establishment of the HD MTX regimen, chemotherapy-alone approaches that omit consolidation RT in patients with CR have been attempted as a curative treatment option for PCNSL. The omission of RT was reported to result in a lower incidence of neurocognitive dysfunction; however, there was an increase in local or intracranial distant recurrence [12, 14–16]. Consequently, consolidation RT again plays a part in the initial treatment of PCNSL.

In discussing the role of the consolidation radiotherapy, the blood–brain barrier (BBB), which may characterize the clinical behavior of PCNSL, must be considered. Both gadolinium (Gd) MRI contrast- and chemotherapeutic agents are blocked by the intact BBB. However, large PCNSL lesions with a disrupted BBB tend to be strongly enhanced on Gd-enhanced MRI scans. Such lesions are expected to be good chemoresponders because the chemotherapeutic agents can permeate into the lesion. On the other hand, extremely small PCNSL lesions that are too small to disrupt the BBB may be undetectable on Gd-enhanced MRI

scans. They may be unaffected by the chemotherapeutic agents and maintain their proliferative capacity even during chemotherapy. Thus, paradoxically, large visible lesions are chemoresponders while small undetected lesions are chemoresistant.

After chemotherapy alone, not a few PCNSL patients may suffer extremely early local recurrence, even after having been judged as CR on posttreatment Gd-enhanced MRI scans [12]. If the BBB recovers from disruption with shrinkage of the tumor and its recovery is complete before tumor cell annihilation, the previously chemoresponsive lesion may turn into a small, residual, chemoresistant lesion undetectable by MRI. It may be "more than microscopic" and consist of a cluster of a viable tumor cells. Regrowth of the post-chemotherapy residual lesion is clinically recognized as early local recurrence. Therefore, the significance of consolidation RT is different in PCNSL and other nodal or extranodal lymphomas because the determination of posttreatment CR is difficult on MRI scans of PCNSL.

As some PCNSLs are multicentric, even when an initial MRI-based diagnosis of solitary PCNSL, consolidation RT should be indicated considering the existence of small, undetectable, chemoresistant lesions beyond an intact BBB. After chemotherapy alone, some PCNSL patients may develop early intracranial distant recurrence. When only one of multiple PCNSL lesions is large enough to be detected on Gd-enhanced MRI scans, the diagnosis should be solitary PCNSL. If BBB disruption persists until total annihilation of the tumor cells by chemotherapy, true CR of this lesion can be achieved by chemotherapy alone. However, subsequently, other small lesions unaffected by chemotherapy may begin to grow, and in such cases the clinical diagnosis should be intracranial distant—without local recurrence. This reenforces the importance of consolidation RT in patients with PCNSL and may warrant the use of WBRT.

1.6.2 RT for Refractory or Recurrent PCNSL After Chemotherapy Alone

Depending on the chemotherapy regimen and patient background, the reported non-CR rate after MTX-based chemotherapy without RT is 22–71% [9, 15–18]. Among patients with CR, 50–81% developed intracranial relapse at the primary tumor site or at a distant site [15, 17, 18]. In patients with refractory or recurrent lesions, salvage treatment with RT or second-line chemotherapy should be considered. RT has been shown to be the most effective salvage treatment [15].

1.6.3 RT for Progressive Disease During Initial Chemotherapy

Approximately 10% of PCNSL patients experience tumor progression during initial MTX-based chemotherapy; their tumors are chemo-resistant and/or aggressively proliferating. In such cases RT should be started immediately to prevent symptomatic worsening.

1.6.4 Re-irradiation for Recurrence After Whole-Brain Radiotherapy

Intracranial relapse is seen in 30–50% of patients who received initial treatment with MTX-based chemotherapy and WBRT. While re-irradiation is a treatment option for the post-WBRT recurrence of PCNSL, repeat-WBRT with curative intent may be appropriate under limited conditions. As the TD5/5 to the whole brain is considered to be 45 Gy [19], re-WBRT after a prolonged interval may be safe if the cumulative dose does not exceed 50 Gy. Theoretically, a protocol with a reduced WBRT dose lower than 25 Gy could be repeated twice although it is unclear whether the second round of WBRT is safe. Since patients with recurrent PCNSL often have received or will receive several courses of salvage chemotherapy with or without MTX, it is difficult to estimate the possible neurotoxicity of re-WBRT. Therefore, partial brain- or local RT with palliative intent is often used for recurrent PCNSL after initial WBRT.

1.6.5 Palliative RT

RT is preferable as a palliative treatment in patients with symptomatic newly diagnosed or recurrent PCNSL because it results in prompt, safe, and long-lasting symptom relief. Partial brain- or local irradiation with a hypofractionated schedule and conventional WBRT is often used for palliative RT. In a subset of patients, single-dose or fractionated stereotactic irradiation may be a treatment option.

1.6.6 RT in Elderly Patients

Advanced age is a major adverse prognostic factor in PCNSL [20]. Among long-term survivors initially treated with WBRT, brain atrophy and neurocognitive dysfunction are more common in elderly than young patients [14, 21–24]. To decrease WBRT-induced neurotoxicity in the elderly with post-chemotherapy CR, consolidation RT can be omitted, the WBRT dose can be decreased, or partial-brain RT rather than WBRT can be administered [9, 25, 26]. However, it remains controversial whether the reduction in neurotoxicity achievable by RT omission or reduction is at the cost of an increase in intracranial recurrence. Not WBRT but also effective chemotherapy and disease progression may result in future neurocognitive dysfunction.

1.6.7 Radiotherapy for Intraocular Involvement by PCNSL

For patients who present with intraocular involvement at the time of a PCNSL diagnosis, the anterior edge of the WBRT field should be extended to include both eyes. In such patients, the intravitreal injection of MTX is often combined with systemic chemotherapy with high-dose MTX.

1.6.8 RT for Primary Intraocular Lymphoma

In patients with primary unilateral intraocular lymphoma without any evidence of intracranial diseases, RT to the involved eyeball, the ipsilateral optic nerve, and the chiasm, with or without intravitreal MTX injection, is recommended. Intraocular lymphoma has been documented to be a part of PCNSL, and it can be bilateral. Prophylactic WBRT or irradiation to the uninvolved eye may not be necessary. If the involved eye is treated appropriately with RT, the incidence of intracranial relapse is not sufficiently high to warrant routine prophylactic WBRT [27]. Patients with intracranial relapse after the treatment of primary intraocular lymphoma may respond well to chemotherapy and RT.

1.7 Radiation Therapy (Treatment Procedures)

A patient with multiple chemo-resistant PCNSL treated with WBRT and boost irradiation is presented in Figs. 1.1, 1.2, 1.3, and 1.4.

1.7.1 RT Planning

Three-dimensional (3D) CT imaging is usually performed in patients with PCNSL for the treatment planning with WBRT or partial-brain RT. Thin-slice CT images of the whole brain down to at least the third cervical vertebral level should be obtained with head fixation with a shell.

The fusion of CT and MR images on a radiation treatment planning (RTP) system is useful especially when partial brain RT is planned. The images to be fused, i.e., pre- and post-chemotherapy MRI scans, Gd-enhanced T1WI scans, and fluid-attenuated inversion recovery (FLAIR) images, should be chosen based on the gross tumor volume (GTV) or the clinical target volume (CTV) of the planned partial brain RT.

1.7.2 Whole-Brain Radiotherapy (Fig. 1.2)

With the exception of some patients requiring palliative RT, WBRT is the standard RT technique for PCNSL [4]. To obtain full coverage of brain tissues, adequate lens sparing, and radiation-dose homogeneity, CT-based 3D RT planning is recommended before the delivery of WBRT.

1.7.2.1 Target Volumes

The gross tumor volume (GTV) is identified on contrast-enhanced MRI scans performed before chemotherapy. It usually does not influence determination of the irradiation field for WBRT. However, superimposition of the GTV on planning CT images is helpful for avoiding unexpected under-dosing at GTV.

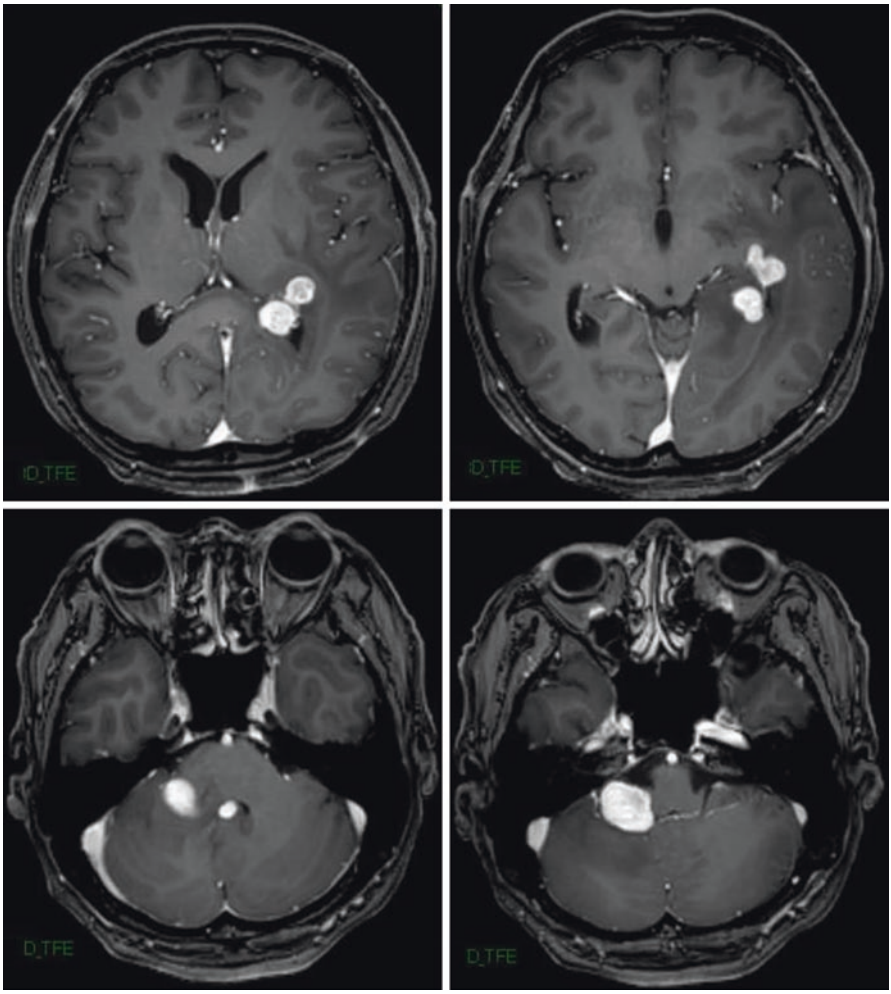

Fig. 1.1 Gadolinium-enhanced MR images of a 58-year-old male with multiple PCNSL presenting with right oculomotor nerve palsy. Two contiguous supratentorial lesions and two contiguous infratentorial lesions are observed. The patient showed symptomatic progression just after one course of high-dose MTX chemotherapy

The clinical target volume (CTV) includes the entire brain parenchyma, several centimeters of the contiguous cervical cord, and the posterior semispherical surface of the eyeballs.

The planning target volume (PTV) is determined by adding a margin ranging from a few millimeters to 1 cm to the CTV.

1.7.2.2 Radiation Field

Two laterally opposite fields are used. The anterior border of the field should include the posterior half of the bilateral eyeballs. The inferior border of the field is usually extended to include the second cervical vertebra. The posterior and superior borders

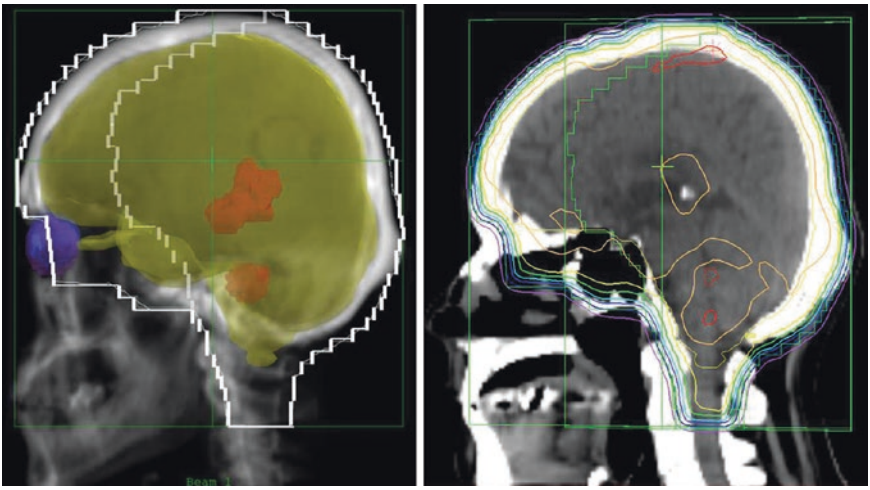

Fig. 1.2 Whole-brain radiotherapy. Two slightly angled laterally opposed 6 MV X-ray beams were used in the field-in-field technique. The GTV, a Gd-enhanced area (*red*), the brain parenchyma (*yellow*), eyeball (*violet*), and lens (*blue*) are superimposed on the beam's-eye-view (*left panel*). The *right panel* shows the dose distribution in a sagittal plane. Isodose (90%, 95%, 100%, and 105%) lines are drawn in *green*, *yellow*, *orange*, and *red*, respectively. In the course of 3 weeks, a total dose of 30 Gy was delivered in 15 fractions to the whole brain

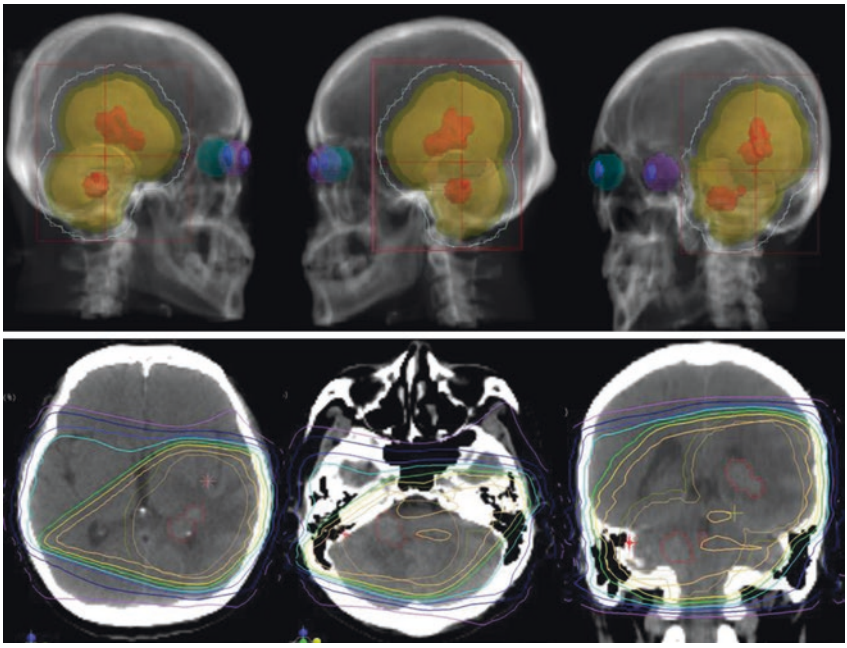

Fig. 1.3 Boost radiotherapy with 3D-CRT using three portal 15 MV X-ray beams. The GTV is displayed as a Gd-enhanced area (*red*). The CTV (*orange*) and PTV (*pale yellow*) are superimposed on the beam's-eye-views (*upper panels*). The *lower panels* show the distribution in the representative planes. A total dose of 10 Gy was delivered in five fractions over the course of 1 week

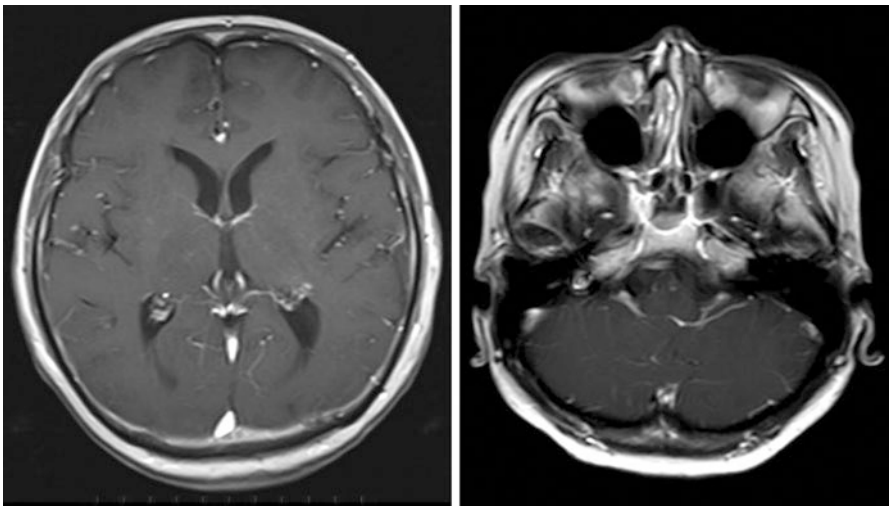

Fig. 1.4 Gd-enhanced MRI scans obtained on the day after the completion of radiotherapy

are set to cover the PTV with an adequate margin, usually a little beyond the outer surface of the skull.

Beam shaping with a multileaf collimator (MLC) is useful for achieving high conformity. The eye lenses are spared by placing the edge of the leaf a few millimeters behind the lenses. For the manual adjustment of the MLC, the leaf position must be selected carefully to minimize possible under-dosing at the tip of the temporal and frontal lobes.

To avoid divergence toward the contralateral eye lens, the beams are often angled so that the anterior beam edges are parallel. As beam angling may deliver an overdose exceeding 110% of the prescribed dose to the anterosuperior portion of the brain, the use of wedges combined with collimator rotation or the field-in-field technique may help to improve homogeneity of the radiation dose.

1.7.2.3 Beam Energy

High-energy photon beams, 6–10 MV X-rays, are used for WBRT.

1.7.2.4 Dose and Fractionation

The recommended WBRT dose for consolidation RT in patients with CR after MTX-based chemotherapy is 23.4–30 Gy; 24 Gy is the standard dose according to the most recent guidelines [4, 9, 10, 16].

Patients with non-CR after chemotherapy or with recurrence after chemotherapy alone are treated with a WBRT dose of 36–45 Gy [4]. The dose must consider the intensity of prior chemotherapy, the patient age, the time lapse since chemotherapy, and the aggressiveness of the tumor estimated from the clinical course.

In patients receiving RT alone as the primary treatment with curative intent, the delivery of at least 40 Gy of WBRT is necessary. Based on the tumor response, up

to 50 Gy of WBRT or 10 Gy of additional boost irradiation to the tumor site may be appropriate. For palliative RT 30 Gy of WBRT is usually effective.

The typical fraction size is 1.5–2 Gy for curative WBRT; 3 Gy or more per fraction are used for palliative or emergency WBRT. Considering the high alpha-beta ratio of lymphoma and the low alpha-beta ratio of the brain, PCNSL is theoretically a good candidate for a hyperfractionated radiation delivery schedule. The Radiation Therapy Oncology Group (RTOG) 9310 study used hyperfractionated WBRT of 1.2 Gy per fraction twice a day up to 36 Gy for consolidation RT [28]. This regimen, however, delayed but did not eliminate severe neurotoxicity.

1.7.3 Partial Brain RT (Fig. 1.3)

To manage PCNSL, partial brain RT is used in limited situations, such as boost irradiation after WBRT to non-CR or recurrent lesions, and as palliative RT for recurrence after initial treatment with WBRT. For the initial treatment of PCNSL, either for consolidation or salvage, partial brain RT is thought to be insufficient despite its potential advantage of reduced neurotoxicity [29]. Iwabuchi et al. [26] reported the results of the initial use of partial brain RT in patients with solitary PCNSL. They suggested that survival was acceptable when compared with patients who had undergone WBRT.

In clinical practice, a boost to the residual tumor is often delivered to improve local control, particularly in cases with incomplete chemotherapy, in patients treated with a reduced WBRT dose, and/or in cases with a solitary and large residual tumor. However, the benefits of adding a boost to WBRT remain controversial.

1.7.3.1 Target Volumes

GTV: For boost irradiation to the residual tumor, the GTV is the contrast-enhanced tumor(s) identified on MRI scans. For contouring the GTV, any MRI scans performed before or after chemotherapy, or after WBRT can be used.

CTV: The CTV adds an adequate margin to the GTV. The GTV-CTV margin can vary from a few millimeters to 3 cm; it is determined by the purpose of partial brain RT and institutional policies. Including the high-intensity areas on FLAIR images in the CTV is an acceptable option.

PTV: To obtain the PTV, a margin of a few millimeters is added to the CTV.

1.7.3.2 RT Technique

For 3D conformal RT (3D-CRT), multiple 6–15 MV and MLC-shaped X-ray beams from several directions are usually used.

1.7.3.3 Dose

The optimal dose for partial brain RT has not been established. PCNSL patients with non-CR or recurrence after chemotherapy alone are often treated with WBRT without boosting. In such cases, a WBRT dose of 36–45 Gy is recommended [4]. Shibamoto et al. [30] who performed a large-scale retrospective study suggested

that the optimal total dose is 40–49.9 Gy. Consequently, for the WBRT-plus-boost approach, the WBRT dose that does not compromise intracranial disease control should be 24–30 Gy, and the additional boost dose that does not compromise local control should be 10–20 Gy. One of the most practical schedules may be WBRT of 30 Gy in 15–20 fractions followed by partial brain RT with a boost of 10–20 Gy delivered in 5–10 fractions.

1.8 Outcomes

1.8.1 Survival

The 5-year survival rate and the median survival time of PCNSL patients treated with HD MTX and WBRT have been reported to be 30–50% and 36–63 months, respectively [28, 31–33].

1.8.2 Prognostic Factors

The patient age and Karnofsky performance status (KPS) are strong prognostic factors in PCNSL. Recursive partitioning analysis (RPA) incorporating only these two factors showed that the median survival time of class I (age = <50), class II (age > 50, KPS ≥ 70), and class III (Age > 50, KPS < 70) was 8.5-, 3.2-, and 1.1 years, respectively [34]. Other reported prognostic indicators are CR after chemotherapy [33], elevated lactate dehydrogenase- and cerebrospinal fluid protein levels, and tumors in deep regions of the brain [20, 30].

1.9 Toxicity

1.9.1 Acute Toxicity

Alopecia is a common finding in patients with acute WBRT toxicity. Nausea, vomiting, and anorexia tend to be limited to grades 1 and 2. Leukocytopenia may occur, but seldom forces treatment interruption.

1.9.2 Late Toxicity

As the survival of PCNSL patients improved, the incidence of late neurological toxicities, including neurocognitive dysfunction accompanied by leukoencephalopathy or brain atrophy, has become a major concern in patients treated by HD MTX and WBRT. Approaches to reduce late neurological toxicities have mainly focused on minimizing the adverse effects of RT by reducing the WBRT dose with or without boosting, by delivering smaller doses per fraction, by administering

partial brain RT instead of WBRT, and by omitting RT [9, 10, 26, 28]. Additional studies are needed to identify the optimal RT setting to preserve neurocognitive function without compromising intracranial control.

Ocular RT for primary intraocular lymphoma or PNSCL with intraocular involvement consisting of irradiation to the eye lens above 10 Gy often elicits cataracts. Xerophthalmia and dry eye syndrome may develop after the delivery of RT doses exceeding 30 Gy to the conjunctiva or lacrimal glands. Retinopathy and ophthalmic neuropathy are rarely seen at RT doses below 45 Gy [35].

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