

Ependymomas

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Opinion statement

Optimal management of ependymomas includes surgical resection and evaluation of the extent of central nervous system involvement using cerebrospinal fluid cytology and craniospinal contrast-enhanced MRI. In instances of measurable residual disease, reoperation should be considered because survival of patients with ependymomas is significantly improved by performance of a complete resection. In patients not considered for further surgery and with residual disease, limited-field radiotherapy is usually administered. The role of craniospinal irradiation in patients with local disease and no evidence of metastasis is controversial because most tumor recurrences are local and at the site of the primary tumor. No clear role for adjuvant chemotherapy has been demonstrated. When used, chemotherapy for ependymomas has been administered primarily to children aged younger than 3 years as adjuvant therapy and to patients with recurrent disease who are not considered surgical candidates as salvage therapy. Recurrent ependymomas are managed by reoperation of tumors that are surgically accessible, by radiotherapy if not previously administered, and by salvage chemotherapy. The role of stereotactic radiotherapy administered as radiosurgery or brachytherapy is unclear because all reports are anecdotal. Because salvage chemotherapy is not curative, no standard therapy exists, and a variety of chemotherapy agents and drug schedules have been investigated.

Introduction

Ependymomas are tumors that arise from the ependymal cells of the cerebral ventricles, the central canal of the spinal cord, and cortical rests [1–5, Class III]. Ependymomas constitute 8% to 10% of brain tumors in children and 1% to 3% of brain tumors in adults. Sixty percent of ependymomas occur in children who are aged younger than 16 years, and 25% occur in children aged younger than 4 years [6••, Class III]. Tumors arising in the supratentorial compartment (50% to 60% of adult ependymomas, 30% of pediatric ependymomas) most often are hemispheric or occur in relationship to the third ventricle [6••, Class III]. Tumors found in the posterior fossa are seen in a midline fourth ventricular location (40% to 50%) or are paramedian and located in the cerebellopontine angle (50% to 60%) [6••, Class III]. The World Health Organization (WHO) classification of tumors separates ependymomas into subependymomas (WHO grade 1), myxopapillary

ependymomas (WHO grade 1), ependymomas (WHO grade 2), and anaplastic ependymomas (WHO grade 3) [7••, Class I; 8,9, Class III; 10••, Class II; 11,12; Class III]. Ependymoblastomas are considered a different type of tumor, classified under embryonal primitive neuroectodermal tumors.

Approximately 30% of all intracranial ependymomas are anaplastic, although the prognostic significance of anaplasia is controversial and unclear [13–15, Class III]. Part of this uncertainty relates to the lack of uniform histological criteria for diagnosing anaplastic ependymomas. Defining tumors as anaplastic based on proliferation indices such as Ki67 staining more than 1% may permit stratification of patients at high risk for recurrence and decreased survival [13–15, Class III].

Cerebrospinal fluid (CSF) dissemination occurs in 3% to 12% of all intracranial ependymomas and is most frequent in patients with infratentorial anaplastic

ependymomas [7••, Class I; 8,13,14,16,17,18••, Class III]. Because a small but measurable risk for CSF dissemination exists for all patients with newly diagnosed ependymoma, an extent of disease evaluation including CSF cytology and craniospinal MRI is mandated after surgery [11, Class III]. This staging permits stratification of patients into those with (M+) or without metastasis (M₀) and with or without residual disease after surgery, the two most important clinical parameters affecting outcome.

Little is known about the genetic alterations of ependymomas. Kraus [19, Class III] described frequent loss of chromosome 22q in adults (not involving the NF2 gene), whereas in children, loss is more commonly seen on chromosome 1, 17p, and 6q. Korshunov et al. [20, Class III] described p14^{arf} loss in ependymomas that correlated with increasing anaplasia. Unlike gliomas, ependymomas rarely demonstrate p53 mutations. Gilbertson et al. [21, Class III] have suggested that epidermal growth factor receptor signaling results in aggressive disease behavior in ependymoma by promoting tumor cell proliferation. This may represent a potential novel target for future therapies.

INTRACRANIAL EPENDYMOMA

The clinical presentation of intracranial ependymomas most often is composed of signs and symptoms of raised intracranial pressure (headache, alteration in level of consciousness, nausea/vomiting, diplopia, papilledema, gait instability, and meningismus) because of tumor mass effect or obstructive hydrocephalus [22, Class III]. Treatment of ependymomas is primarily surgical because essentially all analyses have determined that completeness of surgical resection is the most important covariant affecting progression-free and overall survival [7••, Class I; 8, Class III; 10••, Class II; 11,13,17,23, Class III]. As a consequence, reoperation after initial incomplete surgery or at time of tumor recurrence is advocated assuming that a complete resection is achievable [23, Class III]. Gross total resection is dependent on the operator and infiltration of tumor into eloquent areas of brain. For example, lateral infratentorial ependymomas often infiltrate surrounding cranial nerves and invade the brainstem, making complete resection technically more difficult and more likely if performed to result in significant neurologic morbidity [24, Class III]. As a consequence, reports of achieving a gross total resection vary from 50% to 75%. Paulino et al. [25, Class III], in a series of 49 patients with intracranial ependymomas, report local control rates at 5, 10, and 15 years of 75.1% after image-verified complete resection, compared with 49.2%, 41.6%, and 35.6% after incomplete resection. After surgery, the issue of how often to image patients is unclear. Good et al. [26, Class III] suggested that regular surveillance neuroimaging revealed that 43% of all recurrences were asymptomatic and that recurrences occurred with a

median time of 14.5 months (range 3–65 months). Regular surveillance appeared to favorably impact survival and subsequent treatment, in particular, the ability to perform a reoperation with complete resection.

Robertson et al. [7••, Class I] described the extent of surgical resection and the amount of residual tumor on postoperative MRI as being the only predictor of a longer progression-free survival duration. Healey et al. [23, Class III] described the presence of radiographic residual disease on postoperative imaging as the most important prognostic variable for intracranial ependymomas. Rogers et al. [27••, Class III] described postoperative complications of resection of infratentorial ependymomas in adults in which new cranial nerve deficits occurred in 33%; 26.6% of patients developed dysphagia requiring a gastrostomy tube, infectious complications occurred in 13.3%, and 4.4% of patients died perioperatively. Many of these deficits recovered with time. In addition, the posterior fossa syndrome (cerebellar mutism) after an infratentorial craniotomy in children is a well-defined although infrequent complication [28, Class III].

Radiotherapy represents the second most frequently used adjuvant treatment modality for ependymomas despite the lack of a randomized clinical trial showing benefit and the general consensus that ependymomas are radioresistant [7••, Class I; 8,11,13,14,17,25,29,30, Class III]. Furthermore, there are no data regarding a dose-response relationship in ependymomas, and as such, total tumor dose has varied. By consensus, many radiation oncologists think a tumor dose exceeding 45 Gy is necessary, and most advocate a tumor dose of 54 to 55 Gy for ependymomas and 60 Gy for anaplastic ependymomas [29, Class III]. Because of the possibility of CSF spread, one of the controversies regarding the radiotherapeutic management of ependymomas is the volume of brain that needs to be treated. Notwithstanding early enthusiasm for craniospinal irradiation (CSI), several recent studies support the application of limited-field radiotherapy for M₀ tumors and reserve CSI for M+ tumors [11,14,25,29,31, Class III]. Paulino et al. [25, Class III], as do others, report 5-, 10-, and 15-year overall survival rates of 71.4%, 65.3%, and 63.5%, respectively, after CSI and 80.8%, 64.6%, and 64.6%, respectively, after local-field radiotherapy in patients with M₀ disease. In addition, there are advocates for observation only after gross total resection (ie, withholding radiotherapy) for supratentorial ependymomas; however, this suggestion is based on case series and has not been rigorously evaluated [30, Class III]. Lastly, conformal radiotherapy, including stereotactic radiotherapy, is increasingly used despite the paucity of studies showing benefit [13,32, Class III]. Limiting the tumor treatment volume by way of conformal radiotherapy is theoretically appealing because irradiation of normal tissue is avoided and presumably delayed late radiation injury is mitigated.

Table 1. Adjuvant chemotherapy trials in ependymoma

Study	Patients, <i>n</i>	Chemotherapy regimen	PFS	OS
Duffner et al. [34, Class III]	66	Cyclophosphamide + vincristine/cisplatin + etoposide	41% at 1 year	NR
Needle et al. [52]	19	Carboplatin + vincristine/ifosfamide + etoposide	74% at 5 years	NR
Robertson et al. [7••, Class I]	32	Randomized to lomustine + vincristine + prednisone or "eight in one" regimen	50% at 5 years	64% at 5 years
Grill et al. [10••, Class II]	73	Procarbazine + carboplatin/etoposide + cisplatin/vincristine + cyclophosphamide	22% at 4 years	59% at 4 years
Van Veelen-Vincent et al. [11, Class III]	83	Procarbazine + carboplatin/etoposide + cisplatin/vincristine + cyclophosphamide	48% at 5 years; 46% at 10 years	68% at 5 years; 47% at 10 years
Ziegler et al. [53]	8	Cyclophosphamide + vincristine + etoposide	13% at 3 years	32% at 3 years

"Eight in one" regimen—etoposide + carboplatin + PCV (procarbazine, lomustine, and vincristine) + MOPP (mechlorethamine + vincristine + prednisone + procarbazine) alternating with cyclophosphamide + vincristine + cisplatin + etoposide + autologous bone marrow transplantation; NR—not reported; OS—overall survival; PFS—progression-free survival.

However, there are no randomized trials that have demonstrated clear benefit with regard to survival or quality of life. Boost radiotherapy, in which additional radiotherapy is administered adjunctively most often by way of a stereotactic methodology (eg, by LINAC radiosurgery, Gamma Knife, or CyberKnife) after conventional radiotherapy of the primary tumor, is increasingly used outside of clinical trials [13,32 Class III]. This adjuvant treatment is based on the assumption that radioresistance of ependymomas is relative and that by increasing dose to the tumor, radioresistance may be overcome. Also, because most ependymoma treatment failures are local, augmenting tumor radiotherapy dose may improve long-term control. Despite an appealing construct, the lack of an established dose-response relationship for ependymomas after radiotherapy and the empiric observation that measurable neuroradiographic responses are rare suggest more is not necessarily better. A randomized trial evaluating stereotactic radiotherapies would clarify their purported benefits. Further supporting the thesis that more is not necessarily better is a report by Kovnar et al. [33, Class III] on using hyperfractionated radiotherapy as adjuvant radiotherapy for ependymoma, which showed limited benefit when compared with conventionally fractionated radiotherapy.

More controversial is the role of chemotherapy in the management of ependymomas (Table 1). Robertson et al. [7••, Class I] reported a prospective trial involving 32 children with newly diagnosed intracranial ependymoma that examined the role of adjuvant chemotherapy (lomustine, vincristine, and prednisone vs so-called "eight in one" regimen) after initial surgery and CSI. This multi-institutional Children's Cancer Group study demonstrated that the extent of surgical resection and volume of residual disease on postoperative imaging predict for progression-free survival. Chemotherapy had no impact on progression-free survival with either chemotherapy drug regimen. Five-year progression-free survival and overall

survival rates were 50% and 64%, respectively. Most relapses were local treatment failures (71%) or concurrent local and distant central nervous system (CNS) metastasis (21%), and isolated metastatic relapse was uncommon (7%) and occurred only in the setting of M+ disease at diagnosis. The study concluded that involved-field radiotherapy results in similar outcomes compared with CSI, and therefore CSI is appropriately reserved for disseminated neuraxis disease (M+).

In a report of 48 infants with newly diagnosed intracranial ependymoma from the Pediatric Oncology Group, Duffner et al. [17,34 Class III] demonstrated a 48% response (partial and complete) to adjuvant cyclophosphamide and vincristine cycled with cisplatin and etoposide. Furthermore, when evaluating outcome as a function of timing of radiotherapy (at 1 year in children aged 2–3 years and at 2 years in children aged 1–2 years), 5-year survival was negatively affected by delaying irradiation (63% vs 26%). This study suggests modest efficacy of adjuvant chemotherapy after initial surgery; however, chemotherapy appears inferior to the benefit seen by administration of radiotherapy.

Van Veelen-Vincent et al. [11, Class III] reported a retrospective review of 83 children with newly diagnosed intracranial ependymomas treated with surgery (73% gross total resection), limited-field radiotherapy (in all ages before 1990, in children aged older than 3 years from 1990–1995, and in children aged older than 5 years after 1995), and multiagent chemotherapy. Chemotherapy comprised seven cycles of three chemotherapy courses alternating two drugs at each course (procarbazine and carboplatin, etoposide and cisplatin, vincristine and cyclophosphamide). Considering the group as a whole, overall survival was 68% at 5 years and 47% at 10 years. Event-free survival was 48% at 5 years and 46% at 10 years, with more than 90% of all recurrences occurring in the first 5 years after surgery. Survival after recurrence was 14% at 5 years. Extent of

Table 2. Salvage chemotherapy trials in ependymoma

Study	Patients, <i>n</i>	Chemotherapy regimen	RR	SD
Chiu et al. [55]	12	Procarbazine, lomustine, and vincristine	15%	NR
Grill et al. [59]	16	High-dose chemotherapy + autologous bone marrow transplantation	0%	63%
Needle et al. [56]	5	Etoposide	40%	NR
Mason et al. [18••, Class III]	15	High-dose chemotherapy + autologous bone marrow transplantation	0%	0%
Gornet et al. [57]	16	Platinum or nitrosourea	67% and 25%	30% and 50%
Chamberlain [58]	12	Etoposide	17%	30%
Hurwitz et al. [60]	13	Paclitaxel	6%	37%
Chamberlain [54]	10 (spinal cord ependymoma)	Etoposide	20%	50%
Brandes et al. [35••, Class III]	13	Cisplatin	30%	46%

NR—not reported; RR—response rate; SD—stable disease.

surgery and inclusion of radiotherapy were found on multivariate analysis to predict for improved survival and event-free survival. A gross total resection was found to be the most important prognostic factor, as has been shown in other studies (5-year survival after complete resection was 80%, compared with 51% after incomplete resection). In addition, event-free survival (sometimes referred to as progression-free survival) was 53% after gross total resection versus 33% after subtotal resection, supporting the contention that complete resection lowers the risk of recurrence. In patients treated with chemotherapy after surgery, 5-year survival was 33%, compared with more than 60% in patients treated with radiotherapy, suggesting that the role of primary chemotherapy (in lieu of radiotherapy) is not warranted and that the role of adjuvant chemotherapy is uncertain. Forty-seven percent of patients relapsed, with a mean time to recurrence of 27 months after surgery in which 85% were local recurrences, 8% were local and distant metastases, and an isolated distant metastasis was seen in only one patient (3%). These data again support the position of limited-field radiotherapy in patients initially staged as M₀.

A variety of studies indicate that chemotherapy has a modest effect in the setting of recurrent disease and that no chemotherapy regimen has clear superiority over another (Table 2). Furthermore, dose-intensive chemotherapy offers no advantages over conventional-dose chemotherapy in the treatment of recurrent intracranial ependymomas [18••, Class III].

The management of recurrent ependymoma has not received much attention in the literature despite the fact that nearly 50% of patients will recur. Goldwein et al. [8, Class III] reported on 36 patients with recurrent intracranial ependymoma in which 33 were treated with reoperation, 12 received radiotherapy (not stereotactic radiotherapy), and all received chemotherapy.

Median time to recurrence was 2.8 years, and in most, relapse was local (78%) or local with concomitant distant metastasis (14%). Twenty-nine (79%) of the initial cohort had a second relapse in which a local component to the relapse was seen in 80%. Two-year overall survival and progression-free survival were 29% and 23%, respectively. Considering only first relapse, 2-year actuarial survival was 39%, and median survival was 17 months. Median progression-free survival was 12 months. Among 36 evaluable patients and 37 chemotherapy regimens, there was one partial response (3%), seven patients with stable disease (20%), and 29 disease progressions (77%). In responding or stable disease patients, median duration of response was 9 months (range 3–23 months). Cisplatin was thought to be the most active agent amongst the four commonly used chemotherapeutics (cisplatin, procarbazine, lomustine, and vincristine) [35••, Class III].

SPINAL CORD EPENDYMOMA

Spinal cord tumors are uncommon primary malignancies of the CNS and constitute 5% to 10% of all primary CNS malignancies [36–43, Class III]. Approximately 60% of all primary spinal cord tumors are intradural extramedullary in location and are meningiomas (50%) or peripheral nerve sheath tumors (10%). Intradural intramedullary spinal cord tumors constitute only 30% to 40% of all primary spinal cord tumors, of which ependymomas comprise 60% in adults and 30% in children. Two distinct spinal cord ependymomas occur: 1) the myxopapillary histiotype, which accounts for 50% of all spinal cord ependymomas and is located in the cauda equina with occasional extension into the conus medullaris [36–43, Class III]; and 2) the cellular ependymomas found in the spinal cord proper and which account for 50% of all spinal cord ependymomas. These latter tumors are most often located in the cervical or thoracic spinal cord.

Ependymomas constitute 4% of all primary CNS malignancies in adults, of which 30% occur in the spinal cord [44, Class III]. Assuming 17,000 new cases of adult primary CNS tumors per year in the United States, approximately 227 new cases of spinal cord ependymoma are seen yearly. Of this number, only 50% (124 new cases per annum) are intradural intramedullary ependymoma, indicating the relative rarity of these tumors [45, Class III]. As a consequence, clinical trials directed at the treatment of spinal cord ependymomas have been nonexistent.

Spinal cord ependymomas may arise at any age but present most frequently in adults aged 20 to 40 years [45,46, Class III]. Ependymomas arise from or extend into the cervical cord in more than 65% of cases. More than 90% of spinal cord ependymomas have a benign pathology, are slow growing, and although unencapsulated, tend to compress adjacent cord parenchyma rather than infiltrate it. Approximately 50% of tumors span three or more vertebral levels. Pain is the most common presenting symptom, seen in more than 70% of patients. Sensory disturbance is the second most common presenting symptom in more than 60% of patients. Limb weakness and bladder/bowel dysfunction are symptoms in 50% and 35% of patients, respectively. Objective neurologic signs are seen in more than 70% of all patients at presentation. These signs include hyperreflexia (in > 65% of patients), motor dysfunction (in > 65%), a sensory level (in 35%), and spasticity (in 35%).

A general consensus regarding management of spinal cord ependymomas has emerged based on institutional

experience. Extent of surgical resection is the strongest covariant predicting survival in patients with spinal cord ependymomas [36–44, Class III]. Gross total removal of a spinal cord ependymoma (achievable in > 70% of patients) may be safely attempted because ependymomas do not appear surgically to infiltrate adjacent neural tissues and accordingly, a surgical interface is present. Surgical outcome is dependent on the preoperative neurological status. Patients with good preoperative status not only encounter less surgical morbidity but in addition have less neurologic dysfunction postoperatively. Radiation therapy does not appear necessary after gross total resection of the tumor because 5- and 10-year survival in excess of 80% is expected in patients with completely resected tumors. In the event of tumor recurrence, reoperation with attempted gross total removal should again be considered. Lastly, subtotally resected spinal cord ependymomas may be palliated by the administration of limited-field radiotherapy. Five- and 10-year survival rates of 60% are reported after radiotherapy.

Less clear is the management of recurrent spinal cord ependymomas having previously failed surgery and radiotherapy [42,47–51, Class III]. Because salvage chemotherapy is not curative, no standard regimens exist. A variety of therapeutics have been used for recurrent intracranial ependymomas, as noted earlier (Table 2). These studies indicate that chemotherapy has a very modest effect in the setting of recurrent intracranial ependymoma and that no chemotherapy regimen has clear superiority over another. How to extrapolate these data to recurrent intradural intramedullary ependymomas is problematic.

Treatment

Surgery

- The most common location for infratentorial ependymomas is the fourth ventricle, hence a suboccipital craniotomy with or without a C1 laminectomy is used. Contraindications include poor cardiac or respiratory risk and other medical comorbidities. Complications include cerebellar mutism and injury to the nuclei of the sixth nerve, the facial colliculi, the mesiolingual fossa, and other lower cranial nerves. Tumoral extension through the foramen of Magendie, into the cisterna magna, and downward into the cervical spinal canal can often be removed because the tumor is usually not adherent to the pia. The cost of surgery is \$35,000 to \$40,000.

Radiation

- For low-grade ependymomas the recommended dose for involved-field radiotherapy is 54 Gy in 30 fractions over 5 weeks. High-grade ependymomas are treated with 59.4 Gy in 33 fractions over 6.5 weeks. CSI is reserved for M+ tumors. Contraindications include prior in-field radiotherapy and young age. Complications include radiation-induced necrosis, leukoencephalopathy, and radiation myelitis. Conformal or stereotactic techniques for fractionated radiation treatment planning and delivery have been effectively adopted by most major centers with the aim of reducing radiation-

induced side effects and potentially increasing the dose of radiation delivered to volume considered at risk. Intensity-modulated radiotherapy costs \$40,000 to \$45,000; three-dimensional conformal radiotherapy costs \$25,000 to \$30,000; CSI costs \$28,000 to \$30,000.

Chemotherapy

- No role outside of infant adjuvant trials, investigational trials, and for recurrent ependymomas having failed previous radiotherapy.

Pharmacologic treatment

Etoposide

Standard dosage	50 mg/m ² /day administered orally. May be given as 100 mg/m ² intravenously every 21 days, often in combination with other agents.
Contraindications	Hypersensitivity to drug or components. Severe myelosuppression.
Main drug interactions	Inhibitors of cytochrome P450 3A4 may increase serum etoposide concentrations. Grapefruit juice coingestion may decrease absorption.
Main side effects	Alopecia, diarrhea, anorexia, nausea/vomiting, myelosuppression, hypoalbuminemia may increase toxicity, secondary leukemia.
Special points	Store capsules in refrigeration. Patient variability in bioavailability is common. Stability of intravenous product decreases as concentration increases. Hypotension with rapid intravenous infusion. Administer 75% of dose if glomerular filtration rate (GFR) is 10–50 mL/minute, and administer 50% of dose if GFR < 10 mL/minute. Administer 50% of dose if total bilirubin is 1.5–3 mg/dL or aspartate aminotransferase (AST) is 60–180 U/L, and administer 25% of dose if total bilirubin is 3–5 mg/dL or AST > 180 U/L.
Cost/cost effectiveness	Etoposide costs \$3826.15 (oral) and \$33.84 (intravenous).

Carboplatin

Standard dosage	Adult and pediatric dose: target area under the curve (AUC) 4–6; see accompanying formulas.
Contraindications	Hypersensitivity to drug or components. Pre-existing myelosuppression or thrombocytopenia.
Main drug interactions	Concurrent nephrotoxins, such as aminoglycosides.
Main side effects	Thrombocytopenia is dose-limiting toxicity. Myelosuppression, nausea/vomiting, electrolyte abnormalities.
Special points	Formula for determining pediatric dose: dose (mg/m ²) = target AUC × ([GFR × 0.93] + 15). Note that formula is for mg/m ² , not mg. Formula for determining adult dose (ie, Calvert formula): dose (mg) = target AUC × (GFR + 25). Note that dose is calculated as mg, not mg/m ² . Adult dose uses Cockcroft-Gault formula for determining GFR. Carboplatin is often used in the setting of a multiagent regimen. Aggressive hydration not required. Patients receiving > six cycles of carboplatin may be at greater risk for hypersensitivity reactions.
Cost/cost effectiveness	Carboplatin costs \$1720.20.

Cisplatin

Standard dosage	100–120 mg/m ² intravenously every 21 days.
Contraindications	Hypersensitivity to drug or components. Myelosuppression. Pre-existing renal insufficiency or hearing impairment.
Main drug interactions	Loop diuretics and concurrent nephrotoxins, such as aminoglycosides.
Main side effects	Nephrotoxicity, severe electrolyte disturbances, nausea/vomiting (emetogenic level 5), peripheral neuropathy with cumulative dosing, and irreversible high-frequency hearing loss.

Special points Hydration is required before and after cisplatin. Commonly, hydration will include potassium and magnesium. May consider augmenting urine output by also administering mannitol 12.5 g before and 25 g after cisplatin. Cisplatin must be diluted in sodium-containing fluid; never use dextrose as diluent. Do not refrigerate reconstituted product. Aggressive antiemetic therapy and electrolyte monitoring are required. Nausea may be acute and delayed. Conflicting data exist for dose adjustment for renal impairment. If GFR 10–50 mL/minute, administer 50% of dose. If GFR < 10 mL/minute, do not administer.

Cost/cost effectiveness Cisplatin costs \$419.28.

Vincristine

Standard dosage 1.4 mg/m², maximum of 2 mg/dose intravenously administered weekly.

Contraindications Hypersensitivity to drug or components. Intrathecal administration. Charcot-Marie-Tooth syndrome.

Main drug interactions Cytochrome P450 3A4 inhibitors may increase vincristine serum concentrations. Cytochrome P450 3A4 inducers may decrease vincristine serum concentrations.

Main side effects Neuropathy is dose-limiting toxicity; may be peripheral or autonomic neuropathy. Alopecia.

Special points Vesicant—administer through running intravenous line. Fatal if administered intrathecally. Consider bowel regimen, especially if patient on concurrent narcotics or anticholinergics. Reduce dose by 50% if total bilirubin 1.5–3 mg/dL; reduce dose by 75% if total bilirubin > 3 mg/dL.

Cost/cost effectiveness Vincristine costs \$37.63.

Ifosfamide

Standard dosage Varies greatly (1000–3500 mg intravenously/day).

Contraindications Hypersensitivity to drug or components. Pre-existing myelosuppression.

Main drug interactions May increase activity of warfarin.

Main side effects Hemorrhagic cystitis, neurologic manifestations, myelosuppression, nausea/vomiting, and alopecia.

Special points Must always be administered with mesna. Mesna is given in a 1:1 manner or as 60% of ifosfamide dose divided in three doses at hours 0, 4, and 8. Change in neurologic status requires immediate discontinuation of ifosfamide and institution of methylene blue. Administer 75% of dose if GFR is 10–50 mL/minute; administer 50% of dose if GFR < 10 mL/minute.

Cost/cost effectiveness Ifosfamide costs \$560.66 (mesna costs \$3916.80).

Cyclophosphamide

Standard dosage 750–1500 mg/m² intravenously every 4 weeks.

Contraindications Hypersensitivity to drug or components. Severe bone marrow depression.

Main drug interactions Allopurinol may increase toxicity. Strong cytochrome P450 3A4 inhibitors may reduce activity of cyclophosphamide. Cytochrome P450 3A4 inducers may increase activity of cyclophosphamide.

Main side effects Hemorrhagic cystitis, nausea/vomiting, myelosuppression, cardiomyopathy, alopecia, and sterility.

Special points Maintain vigorous hydration and urine output. May consider mesna if vigorous hydration not possible. No clear recommendations for dose adjustment for renal dysfunction. Consider using 75% of dose if GFR is 10–50 mL/minute and 50% of dose if GFR < 10 mL/minute.

Cost/cost effectiveness Cyclophosphamide costs \$87.43.

Lomustine

Standard dosage 110 mg/m² orally on day 1 of each cycle of procarbazine, lomustine, and vincristine.

Contraindications Hypersensitivity to nitrosoureas, pulmonary fibrosis.

Main drug interactions	Phenobarbital may decrease efficacy of lomustine.
Main side effects	Nausea/vomiting, delayed myelosuppression, pulmonary fibrosis.
Special points	Administer on empty stomach to reduce nausea, usually at bedtime. Round dose to nearest capsule size (available as 10 mg, 40 mg, and 100 mg). Discontinue once cumulative lifetime dose reaches 1400 mg/m ² . Also referred to as "CCNU."
Cost/cost effectiveness	Lomustine costs \$70.48.

Procarbazine

Standard dosage	60 mg/m ² on days 8–21 of each cycle of procarbazine, lomustine, and vincristine.
Contraindications	Hypersensitivity to drug or components. Pre-existing myelosuppression.
Main drug interactions	Disulfiram-like reaction with alcohol. Tricyclic antidepressants and sympathomimetics may induce hypertensive crisis.
Main side effects	CNS depression, nausea/vomiting, delayed myelosuppression, photosensitivity.
Special points	Dose based on dry weight if obese or severe edema/anasarca. Weak monoamine oxidase inhibitor; avoid tyramine-containing foods. Administer as single dose at bedtime. Available as 50-mg capsule; round dose to nearest 50 mg. Consider dose adjustment if serum creatinine > 2 mg/dL or total bilirubin > 3 mg/dL, although no guidelines exist.
Cost/cost effectiveness	Procarbazine costs \$19.49.

Emerging therapies

- Stereotactic radiosurgery has been administered to manage recurrent or residual intracranial tumor in some institutions. This mode of radiotherapy has to be further studied in prospective trials.
- Advances in molecular oncology are likely to provide a better understanding of ependymomas and define molecular targets.

Physical/speech therapy and exercise

- Patients recovering from surgery benefit from a comprehensive physical therapy and exercise plan when clinically indicated.
- In an attempt to achieve maximal resection, neurologic deficits such as cranial nerve deficits may develop. Speech therapy, swallowing evaluation, and retraining become important. Cerebellar mutism, albeit partially self-correcting, may require rehabilitation as well.

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