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SUPPLEMENT ARTICLE

Brain tumors: Medulloblastoma, ATRT, ependymoma

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Abstract

Children with medulloblastoma, atypical teratoid rhabdoid tumor (ATRT), and ependymoma are treated with a multidisciplinary approach including surgery, radiotherapy, and chemotherapy. Lower doses of craniospinal irradiation and tumor bed boost together with chemotherapy are the current standard of care for average-risk medulloblastoma in the Children's Oncology Group (COG). The International Society of Pediatric Oncology (SIOP) is examining the role of hyperfractionated craniospinal irradiation and chemotherapy in high-risk patients. The recent stratification of medulloblastoma into specific molecular risk groups has prompted both COG and SIOP to reexamine the role of these modalities in these different risk groups to maximize cure rates and minimize long-term complications. Proton therapy has shown lower rates of neurocognitive and endocrine complications compared with photons. Ependymomas are treated with maximal surgical resection and adjuvant radiation therapy. The role of chemotherapy in ependymoma is currently being studied in both COG and SIOP. Likewise, for ATRT the role of different high-dose chemotherapy regimens together with local radiation therapy in infants, or craniospinal radiation in older children, is the current focus of research.

KEYWORDS

ATRT, chemotherapy, ependymoma, medulloblastoma, radiation therapy, surgery

1 | INTRODUCTION

Pediatric central nervous system tumors and embryonal malignancies, the most common of which are medulloblastoma and atypical teratoid rhabdoid tumor (ATRT), have an estimated U.S. incidence of 0.62 per 100 000, with 480 new cases in 2018 in patients 0-19 years of age.[1] Ependymomas, considered tumors of glial origin, have an incidence of 0.29 per 100 000, with approximately 240 cases in 2018.[1] Their incidence in Europe seems to be very similar with standardized incidence rates of 0.51, 0.15, and 0.33 per 100 000 for medulloblastoma, ATRT, and ependymoma, respectively. Collectively, these tumors pose a significant clinical challenge and require a multidisciplinary approach to treatment, often requiring surgery, radiotherapy (RT), and chemotherapy.

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; COG, Children's Oncology Group; CSI, craniospinal irradiation; D50%, dose to 50% volume; EFS, event-free survival; GTR, gross total resection; Gy, gray; HART, hyperfractionated-accelerated radiotherapy; IGRT, image-guided radiotherapy; MBEN, medulloblastoma with extensive nodularity; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; SIOP, International Society of Pediatric Oncology; STR, subtotal resection.

2 | GENERAL APPROACH TO TREATMENT

The aggressive biology of embryonal tumors and ependymomas typically dictates a trimodality approach of surgery, chemotherapy, and postoperative RT. In these tumors, maximal safe resection is warranted and has been associated with improved outcomes,[2-5] although more recent data indicate that this may be subtype specific.[6] Evaluation of the craniospinal axis with dedicated MRI imaging of the brain and lumbar puncture for CSF analysis is necessary to fully stage extent of disease and informs the intensity of these therapies. Between 25% and 40% of patients have some form of posterior fossa syndrome, characterized by the triad of mutism, emotional lability, and ataxia, which can lead to long-term neuropsychiatric sequelae.[7]

3 | ROLE OF SURGERY

Surgery, with the intent to achieve a maximal gross total resection (GTR), continues to play an important role in the upfront management of embryonal tumors. In medulloblastoma, residual disease $> 1.5\ cm^2$ has traditionally been associated with inferior disease control in the pre-molecular era.[8,9] However, the recent stratification of medulloblastoma into specific molecular risk groups (WNT, SHH, group 3, and group 4) has reinvigorated the debate about the need for aggressive second look surgeries. Thompson et al. showed that residual disease is implicated only in worse progression-free survival (PFS) in group 4 patients and therefore concluded that while maximal safe resection should still be the goal of surgery, it should not be aggressively pursued at the cost of undue morbidity.[10] Likewise, in ATRT, GTR is also a worthwhile goal and is associated with improved outcomes over those with significant residual disease.[11]

Two-thirds of intracranial pediatric ependymomas arise in the posterior fossa and can be very difficult to grossly resect given the intimate investment of the tumor with the lower cranial nerves. The extent of resection has been identified as the most important prognostic factor in several prospective and retrospective studies.[12-18] Molecular profiling of pediatric ependymomas may be prognostic but early studies indicate that irrespective of subtype (EPN_PFA and EPN_PFB subgroups), both molecular subgroups benefit from maximal safe resection. Furthermore, EPN_PFA tumors have an especially poor survival with subtotal resection (STR).[16,19]

4 | ROLE OF RADIOTHERAPY

RT plays an integral role in the postoperative management of embryonal tumors and pediatric ependymomas, and significant advances in image-guided RT (IGRT) and the development of proton RT have enabled precise and conformal delivery of RT.

In medulloblastoma, craniospinal irradiation (CSI) is standard due to the propensity for failure along the neuroaxis when CSI is omitted.[20] The profound neurocognitive and developmental delays associated with CSI have inspired pediatric oncologists to reduce dose to the neuroaxis. Although initial studies by the pediatric oncology group showed increased relapse with reduction in CSI dose from 36 Gy to 23.4 Gy when chemotherapy was not added,[21] subsequent studies by Packer et al. showed excellent event-free survival (EFS) for combined modality reduced dose CSI (23.4 Gy) with chemotherapy in average-risk patients.[9,22] The latter was also confirmed in European trials.[23] A hyperfractionated RT regimen, applied in the International Society of Pediatric Oncology (SIOP) PNET-4 study, was not associated with an improved survival compared with normofractionated RT.[24] For high-risk patients, a CSI dose of 36 Gy followed by a tumor bed boost to 54 Gy combined with concurrent and consolidative chemotherapy is the current standard of care. A phase I/II study by the Children's Oncology Group (COG) demonstrated a five-year PFS of 59%-71%, depending on whether they were treated on either regimen A or regimen B, with concurrent daily carboplatin and weekly vincristine during RT followed by six months of maintenance chemotherapy with cyclophosphamide and VCR.[25] Anaplastic/large cell histologic variant was found to be a negative prognostic factor however. Comparable data on metastatic medulloblastomas were published in Germany receiving an escalated, hyperfractionated CSI dose of 40 Gy total dose combined with intensive induction and maintenance chemotherapy. For this cohort of 123 patients, five-year PFS and OS were 62% and 72%, respectively.[26] In Italy, a hyperfractionated-accelerated RT regimen (CSI dose 31.2-39 Gy based on patient age), and delivered after intensive sequential chemotherapy, was investigated in a prospective, single-institution study enrolling 33 patients. With a median follow-up of 82 months, the five-year PFS and OS rates were 72% and 73%, respectively. This RT approach will be further investigated, through a three-arm randomization, in the new SIOP High-Risk Medulloblastoma trial that will open soon.

Although published in abstract form only, COG ACNS 0331 reported that a smaller tumor bed boost after CSI showed comparable local control and OS compared with larger whole posterior fossa boost (54 Gy).[27] In the same randomized study, the trial of reduced CSI RT dose to 18 Gy in average-risk patients between three and seven years showed an increased risk of relapse of 10%.[28] COG study ACNS 1422 is evaluating whether both chemotherapy intensity and CSI dose (18 Gy) can be reduced in patients with average-risk WNT-driven tumors who have positive β-catenin and presence of *CTNNB1* [exon 3] mutation) and without large cell/anaplastic medulloblastoma or *MYC/MYCN* amplification and the absence of residual disease ($> 1\ cm^2$). In Europe, the ongoing SIOP PNET-5 study is investigating the possibility to deliver, within a combined modality approach, a reduced CSI dose of 18 Gy to a selected subgroup of children with a low-risk biological profile (ClinicalTrials.gov Identifier: NCT02066220).

Importantly, the duration of RT delivery has been shown to inversely correlate with outcomes in medulloblastoma. Two studies, by Paulino et al. and Del Charco et al., established the importance of keeping RT duration as compressed as possible, ideally to < 46 days.[2,29] Taylor et al. demonstrated an inferior EFS in patients who had prolonged RT duration in the European PNET-3 study.[30]

The improved survival seen in patients with medulloblastoma over the last two decades has renewed efforts to reduce toxicity with highly conformal proton RT. Investigators at Massachusetts General Hospital (MGH) reported results of a phase II trial of proton RT in pediatric medulloblastoma and demonstrated low rates of ototoxicity and more favorable neurocognitive outcomes compared with published photon cohorts while maintaining excellent EFS and OS. Furthermore, other late side effects noted in photon-treated cohorts, such as cardiac, pulmonary, and other late effects, were notably absent in the proton-treated cohort.[31] Vatner et al. recently showed a definitive dose-response relationship between RT dose to the hypothalamus and pituitary and the risk of endocrine deficiency (particularly growth [GH] and thyroid hormone deficiency) in patients treated with proton RT, with a steep rise when dose was > 40 GyRBE.[32] Significantly, the cumulative incidence of GH deficiency (33.3%) and hypothyroidism (20.1%) compares favorably to rates previously published in a photon cohort by Eaton et al. (57% for GH and 69% for thyroid hormone deficiency).[33]

ATRT typically affects very young patients who are most adversely affected by exposure to RT, but Tekautz et al. demonstrated a distinct improvement in disease control in children treated with RT, with a two-year OS of 90% versus 12% in patients for whom RT was omitted.[34] In a recent meta-analysis, Schrey et al. showed that RT was associated with improved relapsed-free survival and OS.[35] Similar findings were suggested by the data of the European RHABDOID Registry (EU-RHAB) and its German precursors. Their retrospective analysis revealed RT as an independent positive prognostic factor for EFS and OS in children with ATRT.[36] The extent of the radiation field in ATRT remains to be debated. Investigators at the Dana Farber pioneered an ATRT regimen that employs intensive chemotherapy in addition to RT, with RT fields tailored according to the age of the patient. Children aged <3 received focal RT (54 Gy) and children aged > 3 received CSI (36 Gy) with a boost to the tumor bed to 54 Gy, resulting in a two-year OS of 70%.[11] The COG study, ACNS 0333, which includes focal RT for patients with non-metastatic (M0) ATRT together with high-dose chemotherapy, showed in an interim progress report a two-year EFS of 43% for the entire cohort (birth to 21 years of age) and most importantly a two-year EFS of 39% for patients < 36 months of age.[37,38] In this study, early RT was employed for older children, and toxicity was worse in this cohort receiving early RT with intensive chemotherapy delivered after radiation. Within Europe, a randomized phase III study SIOPE ATRT01 will soon open evaluating the noninferiority of three courses of high-dose chemotherapy compared with focal RT as consolidation therapy in children aged between 12 and 35 months. Local RT with a dose of 54 Gy up to 59.4 Gy will be delivered depending on the extent of surgery. All children above three years of age will receive RT, either local RT alone (in M0 disease) or including CSI (in M1-M3 stages).

The management of infant medulloblastoma poses a unique therapeutic challenge in pediatric neuro-oncology, due to the detrimental effects of CSI on neurocognitive growth and development. Early trials primarily adopted an RT-sparing approach using induction chemotherapy with some success. Duffner et al. prospectively reported on 102 patients under three years of age who were treated postoperatively with two cycles of cyclophosphamide/vincristine followed by one cycle of cisplatin/etoposide and reported a two-year PFS of 41% in patients less than two years of age.[39] A landmark trial by the German HIT SKK'92 group evaluated the combination of intravenous chemotherapy with methotrexate and additional intraventricular methotrexate and showed an excellent five-year PFS of 83% in patients who had complete resection of their tumor versus 50% for patients with residual disease. Notably, leukoencephalopathy was noted on imaging in many patients and those exposed to intrathecal methotrexate had measurable decrements in measures of intelligence.[40] The novel "Head Start" protocols incorporated five cycles of induction chemotherapy followed by myeloablative chemotherapy with stem cell rescue and demonstrated a five-year EFS of 52% for all patients and 70% for patients with a GTR. The "Desmoplastic" subgroup demonstrated the best outcomes, with a five-year EFS and OS of 67% and 78%, respectively.[41] Recently, the SJYC07 trial evaluated a risk-adapted approach and enrolled 81 patients with infant medulloblastoma and stratified treatment based on low-risk (nonmetastatic, GTR, desmoplastic/MBEN), intermediate-risk, and high-risk (metastatic) treatment groups. Patients with low-risk medulloblastoma underwent induction, consolidation, and maintenance chemotherapy, while intermediate-risk patients underwent induction chemotherapy followed by focal RT to the tumor bed (54 Gy). High-risk patients underwent intensified chemotherapy followed by focal RT to the tumor bed. The trial was largely negative in terms of outcomes (five-year EFS of 31% for the entire cohort) and enrollment of the low-risk group was suspended after an interim analysis showed an unacceptable number of events.[42] Although the trial was considered negative, molecular profiling of the tumors was performed and post hoc analysis demonstrated improved PFS for the Sonic Hedgehog (SHH) cohort compared with group 3 or 4 and a difference in PFS based on SHH methylation (SHH-I vs SHH-II). Of note, nearly 75% of patients with SHH-II were able to avoid CSI compared with only 25% of SHH-I. These data suggest that the molecular classification of medulloblastoma may drive the selection and intensity of therapies in future trials.

In intracranial ependymoma, adjuvant RT is associated with EFS and OS between 60%-70% and 80% at five years for patients with near/gross total resection, respectively.[12-16,43] In ACNS0121, the five-year EFS rates were 61.4%, 37.2%, and 68.5% for observation, STR, and near-total resection/GTR groups given immediate postoperative RT, respectively.[16] The typical strategy is to deliver 50.4-59.4 Gy to the tumor bed with a margin. Although studies have shown a benefit to dose escalation to > 50 Gy,[44] current data indicate that there is an increased risk of brainstem injury with higher doses of RT, particularly with protons. Thus, the current COG protocol ACNS 0831 has different brainstem dose constraints for protons (D50% ≤ 52.4 Gy) and photons (D50% ≤ 61 Gy).[45] The current SIOP-EP-II study investigates the role of a hypofractionated boost, 8 Gy in two fractions, to measurable residual disease before tumor bed irradiation in an attempt to improve local control in this subset of children with a worse prognosis (ClinicalTrials.gov Identifier: NCT02265770).

5 | ROLE OF CHEMOTHERAPY

Chemotherapy is an essential adjunct to surgery and RT for medulloblastoma. In average-risk patients, chemotherapy has allowed for reduction in CSI dose, sparing the detrimental neurocognitive side effects seen at higher RT doses.[9] For high-risk patients, adjuvant chemotherapy has been shown to improve disease control.[46] A more recent phase I/II trial by the COG evaluated the use of concurrent carboplatin/vincristine followed by six months of maintenance chemotherapy and demonstrated a five-year 82% OS using this approach.[25] In Europe, patients with high-risk medulloblastoma can soon be enrolled in a randomized trial. After induction chemotherapy, conventional RT, hyperfractionated-accelerated RT (HART) for CSI up to 39.2 Gy in two fractions of 1.3 Gy per day and high-dose chemotherapy followed by conventional RT will be compared. After RT, maintenance therapy will be randomized in those patients who did not receive high-dose chemotherapy upfront.

Chemotherapy is an essential component of the management of ATRT with a few different regimens showing activity. Patients on the head start (HS) III protocol received five cycles of adjuvant chemotherapy, followed by myeloablative chemotherapy and autologous stem cell rescue. The study demonstrated a three-year OS of 26%.[47] Of note, only a small subset of patients received RT in this trial (if between 6 and 10 years old or residual tumor). Although there is no standard treatment paradigm for ATRT, the use of surgery, intensive chemotherapy, and involved field RT for M0 patients is being investigated in the ACNS 0333 trial. Preliminary results show a two-year EFS and OS of 39% and 48%, respectively, significantly improved compared with prior studies.[37,38] The results of the future European SIOPE ATRT01 trial may help to better understand the role of high-dose chemotherapy in the very young patients. Furthermore, sequencing of the chemotherapy prior to the radiation on this study seemed to not affect disease control, but sequencing RT toward the end may improve the toxicity profile.

For patients with ependymoma, chemotherapy for two cycles is used postoperatively to improve the ability to perform a second surgery in patients with an STR. This is the approach in the current COG ACNS 0831 protocol, as well as the previous ACNS 0121 protocol.[16] Studies to date have yet to show a survival benefit to adjuvant or intensified chemotherapy, which suggests the need for more optimal systemic therapy. ACNS 0831 randomizes patients who achieve maximal safe resection to maintenance chemotherapy. This study will also provide guidance on the optimal therapy for supratentorial classic ependymomas and whether these can be safely observed after a GTR. In the SIOP-EP-II study, patients with no evidence of residual disease are randomly assigned to receive 16 weeks of multiagent chemotherapy or observation after irradiation, while patients with residual disease receive preirradiation conventional chemotherapy with or without methotrexate and postirradiation conventional chemotherapy (ClinicalTrials.gov Identifier: NCT02265770).

6 | FUTURE RESEARCH DIRECTIONS

The discovery of distinct molecular subgroups in patients with medulloblastoma and ependymoma[48-50] has led to renewed efforts to further optimize treatment. ACNS 1422 is evaluating whether both chemotherapy intensity and CSI dose can be reduced in patients with WNT pathway average-risk medulloblastoma, a subset with the most favorable prognosis. The SIOP PNET5 study risk stratifies children with nonmetastatic medullobastoma according to their biology, into low-risk (WNT positive with CTNNB1 somatic mutation), standard-risk, and high-risk (WNT positive aged > 16 years, or metastatic or residual tumor) patients. These low-risk patients receive a lower CSI dose of 18 Gy. The standard-risk patients are randomized to RT alone versus concurrent carboplatin chemotherapy with RT while the high-risk WNT patients older than 16 years, with metastases, receive a dose of 36 Gy to CSI (ClinicalTrials.gov Identifier: NCT02066220).

The COG trial ACNS0121 and a prospective trial (SJYC07) from St. Jude demonstrated the importance of 1q gain as a prognostic factor for ependymoma. In patients treated with immediate postoperative radiation therapy, the five-year EFS was 82.2% for 1q− versus 47.4% for 1q+.[16] The impact of molecular subgrouping in ependymoma remains unclear. Neither the PFS nor the OS differed by RELA fusion status or PF-A/PF-B subgrouping in either the COG or St. Jude study.[16,51] With regard to ATRT, effective measures are needed to be able to avoid or delay RT in very young patients. Integration of highly conformal proton beam therapy with biological understanding and prognostication afforded by molecular subgrouping will help guide treatment strategies to optimize the therapeutic ratio in embryonal tumors and ependymomas. These approaches should be evaluated in prospective clinical trials with rigorous comparison groups. It is an exciting time in the field of pediatric oncology as the biological drivers of pediatric cancers are being revealed and translated into rational therapeutic trials.

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