International Journal of Radiation Oncology biology • physics

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Critical Review

Radiation in Central Nervous System Leukemia: Guidelines From the International Lymphoma Radiation Oncology Group

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Received Feb 1, 2018, and in revised form May 8, 2018. Accepted for publication May 20, 2018.

Consensus Statements

- Effective central nervous system (CNS) prophylaxis for acute lymphoid leukemia requires systemic and intrathecal-directed therapy, with radiation therapy (RT) considered rarely and on a case-by-case basis for patients with high-risk features.
- For patients with overt CNS leukemia at diagnosis or those who develop CNS leukemia at the onset of disease relapse, RT should be considered, especially when other CNS-directed therapy has failed.
- For patients undergoing allogeneic hematopoietic stem cell transplantation, comprehensive RT to the CNS should be considered for patients with acute lymphoid leukemia or acute myeloid leukemia who have a history of CNS involvement.
- We recommend a minimal interval of 2 weeks between the last intravenous or intrathecal administration of methotrexate or cytarabine and initiation of CNS-directed RT. However, in cases in which urgent RT is necessary because of symptoms, shorter intervals of 48 to 72 hours may be considered.
- The choice of comprehensive (ie, craniospinal irradiation) or limited RT to the CNS should depend on the expected long-term outcomes for each individual patient.
- High suspicion for therapy-related neurotoxicity should always be maintained for heavily pretreated patients who present with CNS-related symptoms.
- The recommended RT dose can vary from 18 to 24 Gy.

Introduction

Improvements in outcome for adult patients with acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) over the past several decades have resulted from the incorporation of risk-adapted strategies with induction and

Note—An online CME test for this article can be taken at https://academy.astro.org.

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Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 102, No. 1, pp. 53–58, 2018
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2018.05.067

Durable control of systemic disease in blood and bone marrow has significantly improved survival among patients with leukemia, but extramedullary relapse in the central nervous system can still pose therapeutic challenges for which radiation therapy can have an important role. The objective of this document is to discuss the current role of radiation therapy for patients with leukemia in the central nervous system.

maintenance regimens, increased understanding of disease biology, and superior supportive care. These advances have resulted in improved systemic disease control and, therefore, a greater negative impact of central nervous system (CNS) relapse on disease outcome. In patients with ALL, the risk of CNS involvement at diagnosis is relatively low (roughly 3%-7%) (1). However, in the absence of CNS-directed prophylactic therapy, more than half of adult patients with ALL will develop CNS relapse (2). Among patients with AML, CNS disease at diagnosis is rare, occurring in only 1% of patients (3). Historically, CNS relapses in patients with AML have been uncommon but associated with a poor prognosis. For patients with either AML or ALL, achieving CNS control presents a challenge for the multidisciplinary treatment team because of the potential need to balance treatment intensification with the increased risk of toxicity from CNS-directed therapies.

Diagnosis, workup, and rationale

For all patients with newly diagnosed ALL, diagnostic lumbar puncture is the standard of care for evaluating leukemic CNS involvement. For adults with newly diagnosed AML, on the other hand, lumbar punctures are not recommended in the absence of neurologic symptoms. Patients with AML and risk factors for CNS involvement (eg, monocytic differentiation or high white blood cell count [>40,000/μL] at presentation) can undergo lumbar puncture on completion of systemic therapy to document remission.

Radiographic evaluation of patients with neurologic symptoms at diagnosis should include gadolinium-enhanced magnetic resonance imaging (MRI) of the brain and spine. In the absence of neurologic symptoms, diagnostic MRI has no role in the baseline workup for AML or ALL.

For patients with suspected leukemic involvement of the CNS, lumbar puncture with cytologic and flow cytometry analyses should be done in addition to MRI of the craniospinal axis. Flow cytometric analysis can drastically improve the sensitivity of detecting occult leptomeningeal leukemia in cerebrospinal fluid (CSF) (4, 5). The CNS status of patients with AML or ALL is classified as CNS1 (no blasts in the CSF or CSF cytospin preparation, regardless of white blood cell count), CNS2 (<5 white blood cells/μL in the presence of blast cells in the cytospin), or CNS3 (≥5 white blood cells/μL in CSF with blasts in the cytospin or clinical signs of CNS involvement).

Radiation therapy for CNS prophylaxis for patients with ALL in the absence of a planned transplant

Risk factors for CNS involvement in patients with ALL include elevated lactate dehydrogenase levels, mature B cell subtype, high leukemic cell proliferation index, and T-cell immunophenotype (4, 6, 7). For patients with ALL and no evidence of CNS involvement, the use of radiation therapy (RT) as prophylaxis has largely fallen out of favor because of concerns regarding complications from cranial RT, such as neurocognitive decline, endocrine abnormalities, and brain necrosis, which have collectively limited the use of whole-brain RT (WBRT) for CNS prophylaxis. Rather, attention was directed toward developing treatment regimens that omitted RT. The 2 main chemotherapy agents used for prophylaxis and treatment of CNS disease are methotrexate and cytarabine. Methotrexate, an antimetabolite that interferes with folic acid metabolism, requires high systemic doses to achieve therapeutic concentrations in the CNS. Cytarabine, administered in high intravenous doses, can also achieve adequate tumoricidal doses in the CNS. Indeed, with highly aggressive multiagent chemotherapeutic regimens such as Hyper−CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) that include both high-dose methotrexate and cytarabine in addition to up to 16 intrathecal treatments without CNS RT, the incidence of CNS relapse in one single-institution study was only 4% among 185 patients (1, 8). Other published series have also demonstrated low rates of CNS relapse with intensive systemic and intrathecal regimens (9, 10).

Because data for adults with ALL are limited, many extrapolate from the pediatric ALL population regarding the potential benefit of cranial RT as CNS prophylaxis. In a recent meta-analysis with aggregated data from more than 16,000 pediatric patients with ALL treated between 1996 and 2007 by 10 cooperative study groups, an increased risk of CNS relapse was appreciated only in a small subgroup of patients with CNS3 disease at diagnosis (11). However, use of WBRT did not affect 5-year mortality rates, which were 22.4% among patients treated with RT versus 20.6% for those without it ($P = .83$). Ample evidence also suggests that CNS relapse rates are low after allogeneic hematopoietic stem cell transplantation (HCT) among patients with ALL or AML with no history of pretransplant CNS involvement. Therefore, routine prophylactic CNS-directed RT before allogeneic HCT is not indicated (12, 13). Notably, some institutions still consider low-dose CNS-directed RT for prophylaxis for patients at high risk of CNS relapse, such as those with a T-cell immunophenotype. A recent report on use of a 6-Gy cranial boost for adults with high-risk ALL undergoing total body irradiation (TBI) showed that this approach was tolerable and may have produced better CNS control (14).

Our consensus conclusion is that RT has a very limited role for CNS prophylaxis in adult patients with ALL because of the efficacy of current induction therapies that incorporate CNS-directed chemotherapy, coupled with concerns regarding neurotoxicity.

RT for relapsed CNS leukemia

Patients with relapsed CNS leukemia are often given systemic therapies similar to those given for CNS prophylaxis,

namely, intravenous and intrathecal methotrexate and cytarabine. However, for recurrent or refractory disease after standard induction or maintenance therapy, CNS-directed RT is often considered. Although the prognosis for such patients is poor, retrospective evidence suggests that more comprehensive radiation fields should be considered (15, 16). For patients undergoing allogeneic HCT, more extensive craniospinal irradiation (CSI) should be considered, as discussed later.

CNS-directed RT before allogeneic HCT

In patients undergoing aggressive therapy with allogeneic HCT for high-risk ALL or AML, choosing a pretransplant therapy that achieves a balance between maximizing disease control and minimizing treatment-related toxicity is of great concern. Although CNS relapses after HCT are rare for patients with either AML or ALL, identifying patients at risk for CNS relapse is a priority given the poor outcomes with salvage therapy for relapse after HCT and because most of the conditioning regimens used do not adequately address the CNS. A major risk factor for CNS relapse after allogeneic HCT is a pretransplant history of CNS involvement (either at diagnosis or relapse) (12, 13, 17-19).

Few studies have directly addressed the potential benefit of CNS RT specifically for adult patients at the highest risk of CNS relapse (14): those with any history of CNS3 involvement. In one study of 648 adult patients with AML undergoing HCT, CNS RT improved outcomes among patients with a history of CNS leukemia (20). Patients who had CNS disease and received RT had an improved 5-year relapse-free survival rate of 32%, which was comparable to that of patients without CNS AML (35%). On the other hand, patients with a history of CNS involvement who received intrathecal chemotherapy alone had a 5-year relapse-free survival rate of only 6%. Walker et al also reported a benefit in CNS leukemia control for patients who received comprehensive RT to the craniospinal axis and went on to receive allogeneic HCT (16).

We advocate consideration of CNS-directed RT before HCT for patients with leukemia and a history of CNS disease (at diagnosis or relapse), even if the CNS leukemia responded fully to systemic and/or intrathecal chemotherapy. We strongly recommend CNS RT for patients with active disease that is refractory to intrathecal or intravenous chemotherapy at the time of transplant. Some evidence exists to suggest that CSI may improve CNS disease control before allogeneic HCT to a greater extent than does WBRT, and therefore CSI could be considered a better RT strategy (21).

Radiation technique and dose

No randomized data exist to compare RT doses for patients treated with gross CNS disease (by CSF cytology and/or radiographically). We recommend a dose of 23.4 Gy in 1.8-Gy fractions. By extrapolation from the pediatric literature, a reduced dose of 18 Gy to the spine can be considered. With regard to the radiation field, few data are available on the appropriate CNS target. In the absence of such data, an effort to reduce acute and chronic toxicity from prophylactic RT in pediatric trials involved reducing the field size from craniospinal to whole brain; this led to wide acceptance of using WBRT sequentially with intrathecal chemotherapy to address leukemic CSF involvement. However, because CSF flow throughout the CNS is dynamic, one might hypothesize that WBRT would be inferior to CSI for eliminating CSF blasts because of inadequate coverage of the entire CSF target. Furthermore, in the pediatric patient population, omission of spinal fields is intended to reduce the risk of growth restriction resulting from radiation dose to vertebral growth plates (22-24). This toxicity is not a concern among the adult leukemia population. Because patients who are candidates for CNS-directed RT often have relapsed disease that, in some cases, is refractory to intrathecal and systemic therapy, and because uncontrolled CNS leukemia is fatal, we encourage the use of CSI for adult patients with adequate performance status when a definitive approach to therapy is recommended. However, WBRT can be given for palliation as well.

WBRT is delivered using equally weighted, opposed lateral beams with 6-MV photons. The field should include the leptomeninges and spaces harboring CSF, including the posterior two-thirds of the globe, the cribriform plate, and the middle temporal fossa. Placing the inferior border at the bottom of C1 or C2 is acceptable (Fig. 1). Daily fractions of 1.8 to 2 Gy fractions are appropriate.

When CSI is planned for patients who are to receive a myeloablative regimen with TBI, the CSI dose should be factored into the TBI and the total should not exceed 24 Gy. The CSI can be delivered with photons (Fig. 2A) or protons (Fig. 2B). For photon-based CSI, treatment can be delivered while the patient is prone or supine, depending on the method used at the treating center. Photon treatment while the patient is prone allows visualization of abutting fields and verification of gaps daily to avoid field overlap.

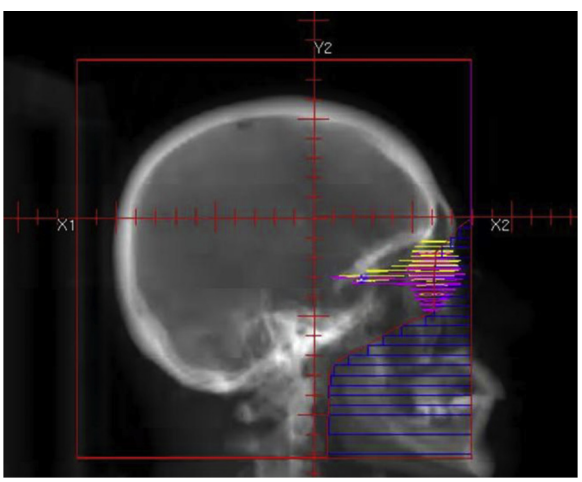

Fig. 1. Treatment fields for whole-brain radiation therapy.

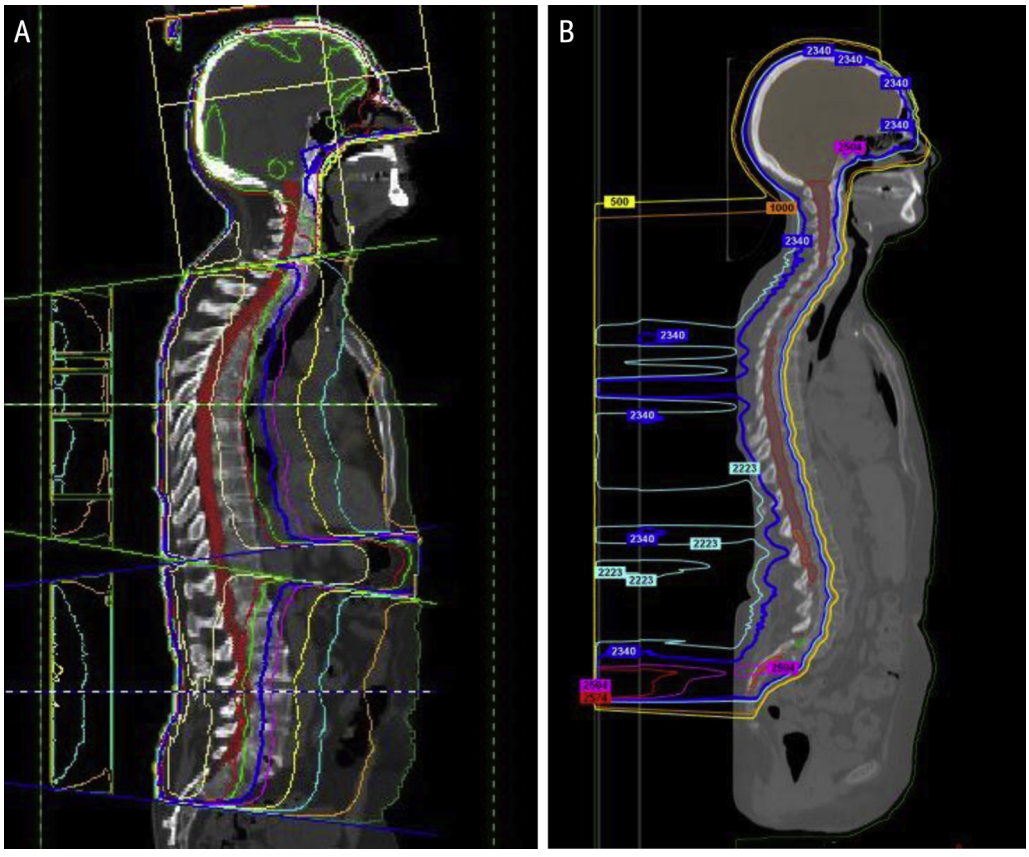

Fig. 2. (A) Dose distribution for photon (x-ray) craniospinal irradiation. (B) Dose distribution for proton craniospinal irradiation.

Patients are often more comfortable, however, in the supine position, and when anesthesia is required (typically for pediatric patients), the supine position may be preferred to facilitate airway access.

Proton-based CSI offers the benefit of anterior dose sparing, which has implications for reducing both acute and chronic toxicity (25-27). However, understanding the key differences in the physical properties of photons and protons is essential for radiation oncologists who use protons for CSI. Many studies have shown an increase in the relative biologic dose at the tail of the Bragg peak that can reach 1.7 for protons (28, 29). Therefore treatment planning should account for this phenomenon, and attention should be paid to ensuring that the posterior distal edge of the beam at the tail of the Bragg peak lands in the middle of the vertebral bodies, beyond the spinal cord, to avoid higher biologic dose within the cord. This is especially important in the areas of abutting spinal fields.

Also essential is accounting for beam range uncertainties derived from differences in tissue densities within beam paths, as well as uncertainties in calculating beam ranges, CT conversion, and daily changes in patient anatomy during treatment relative to simulation; all of these uncertainties can affect the delivery of proton beam therapy. Factors such as these may have minimal effects on CSI delivered with photons, but they should be closely monitored when protons are used.

Toxicity and follow-up considerations

RT is effective for CNS leukemia given the radiosensitivity of leukemia cells and the relatively low doses of radiation required for a tumoricidal effect. However, even low to moderate doses (ie, 18-24 Gy) can lead to toxicity that is more severe than would be expected at such doses, largely because of the synergistic effect of RT and CNS-directed chemotherapy. Historically, WBRT or CSI was delivered concurrently with intrathecal methotrexate and cytarabine; additional follow-up of patients treated with this approach, however, revealed serious toxicities (30). Intrathecal or intravenous chemotherapy with methotrexate, cytarabine, or newer targeted therapies (eg, blinatumomab) has inherent neurotoxic potential and lowers the threshold for neurotoxic effects after RT (31). Therefore, we do not recommend concurrent CNS-directed RT with intrathecal or intravenous chemotherapy. Intrathecal methotrexate has a biphasic elimination pattern, with half-lives of just under 5 hours and 14 hours (32), and large amounts of methotrexate given intravenously can penetrate the CSF (33). Cytarabine, by contrast, has a serum half-life of less than 20 minutes because of its brisk metabolism by hepatic cytidine deaminase (34). These aspects of pharmacology must be considered by treating radiation oncologists in considering the appropriate timing of CNS-directed RT.

We recommend a minimal interval of 48 to 72 hours between the last intravenous or intrathecal dose of methotrexate or cytarabine and initiation of CNS-directed RT; however, longer breaks between methotrexate and CNS-directed RT (3-5 weeks) are more desirable when feasible. In addition to CNS treatment—related encephalopathy, myelopathy is also possible after CNS-directed therapy, even in the absence of RT. Several reports of irreversible dorsal column myelopathy have been reported after intrathecal methotrexate administration (35-37). In 1 series of 13 patients with leukemia who developed myelopathy after intrathecal methotrexate, T2 hyperintensity was observed in the dorsal columns on MRI (38). All of the patients in that study had no evidence of CSF disease but did have elevated CSF protein levels and had received additional CNS-directed therapy, including RT, before the etiology of the symptoms was appreciated. Clinicians should have a high suspicion of toxicity when symptoms of myelopathy are present in the absence of positive CSF findings to avoid additional toxicity from CNS-directed therapy.

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