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CLINICAL INVESTIGATION **Brain**

CONSOLIDATION RADIOTHERAPY IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS: IMPACT ON OUTCOME OF DIFFERENT FIELDS AND DOSES IN PATIENTS IN COMPLETE REMISSION AFTER UPFRONT CHEMOTHERAPY

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Purpose: Avoidance radiotherapy or reduction of irradiation doses in patients with primary central nervous system lymphoma (PCNSL) in complete remission (CR) after high-dose methotrexate (HD-MTX)–based chemotherapy has been proposed to minimize the neurotoxicity risk. Nevertheless, no study has focused on the survival impact of radiation parameters, as far as we know, and the optimal radiation schedule remains to be defined.
Methods and Materials: The impact on outcome and neurologic performance of different radiation fields and doses was assessed in 33 patients with PCNSL who achieved CR after MTX-containing chemotherapy and were referred to consolidation whole-brain irradiation (WBRT). Patterns of relapse were analyzed on computed tomography–guided treatment planning, and neurologic impairment was assessed by the Mini Mental Status Examination.
Results: At a median follow-up of 50 months, 21 patients are relapse-free (5-year failure-free survival [FFS], 51%). WBRT doses ≥40 Gy were not associated with improved disease control in comparison with a WBRT dose of 30 to 36 Gy (relapse rate, 46% vs. 30%; 5-year FFS, 51% vs. 50%; $p = 0.26$). Disease control was not significantly different between patients irradiated to the tumor bed with 45 to 54 Gy or with 36 to 44 Gy, with a 5-year FFS of 35% and 44% ($p = 0.43$), respectively. Twenty patients are alive (5-year overall survival, 54%); WB and tumor bed doses did not have an impact on survival. Impairment as assessed by the Mini Mental Status Examination was significantly more common in patients treated with a WBRT dose ≥40 Gy.
Conclusion: Consolidation with WBRT 36 Gy is advisable in patients with PCNSL in CR after HD-MTX-based chemotherapy. Higher doses do not change the outcome and could increase the risk of neurotoxicity. © 2011 Elsevier Inc.

Radiotherapy, Central nervous system lymphoma, Brain tumor, Local control, Neurotoxicity.

INTRODUCTION

Chemotherapy based on high-dose methotrexate (HD-MTX) followed by whole-brain irradiation (WBRT) is the most commonly used upfront strategy for immunocompetent patients with primary central nervous system lymphoma (PCNSL) (1). According to some authorities, this strategy is associated with an increased risk of severe iatrogenic neurotoxicity, which seems to be strongly related to patient age and WBRT dose. Diverse strategies to reduce the incidence of this disabling complication have been proposed: among others, avoidance of consolidation WBRT in elderly patients in complete remission (CR) after primary chemotherapy, replacement of WBRT with other investigational therapies (*i.e.,* high-dose chemotherapy supported by autologous stem cell transplantation), and reduction of radiotherapy (RT) doses and field extension (1). The latter is consistent with the overall radiation strategy used in limited-stage aggressive lymphomas in past decades. In fact, the large fields used 30 years ago have been replaced by more limited radiation volumes (*i.e.,* involved field) and, more recently, by an ''involved nodal'' approach (2). Similarly, radiation doses were progressively reduced to obtain a more conservative

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Conflict of interest: none.

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approach, with lower incidence of late complications like organ failure or second tumors. Unfortunately, available data on this issue in PCNSL are sparse. A single study has assessed the role of the extension of radiation fields in PCNSL, using partial-brain irradiation instead of WBRT (3), whereas comparative, nonrandomized studies addressing different radiation doses have shown conflicting results (4–6). In the absence of randomized trials comparing consolidation RT with other strategies, optimizing radiation parameters could be an excellent approach to improve outcome and to reduce neurotoxicity incidence in ordinary clinical practice.

In this article, we summarize the findings of a retrospective analysis of consolidation RT in a single-institution series of immunocompetent patients with PCNSL in CR after primary HD-MTX-based chemotherapy. The impact of different radiation fields and doses on local control, survival, and neurotoxicity risk was analyzed to provide treatment recommendations for ordinary clinical practice and to identify crucial questions to be addressed in future prospective trials.

PATIENTS AND METHODS

Study group

This analysis considered HIV-negative adult patients with PCNSL in CR after upfront chemotherapy based on HD-MTX who were referred to consolidation radiotherapy and underwent neuroimaging at diagnosis and follow-up, diagnostic biopsy, and treatment at the San Raffaele H Scientific Institute from 1991 to 2008. The aim of this study was to address the impact on local control, pattern of failure, survival, and neurotoxicity risk of different consolidation radiation fields and doses. Lymphoma diagnosis was histologically confirmed in all cases, and all patients were referred to staging with, at least, contrasted total-body CT scan and bone marrow biopsy. Central nervous system staging was completed with physicochemical analysis and cytologic examination of cerebrospinal fluid (CSF) and ophthalmologic examination with slit lamp. Risk groups were defined according to the prognostic score of the International Extranodal Lymphoma Study Group (IELSG) (7). Neuropsychologic performance was assessed by the Mini Mental Status Examination (MMSE) and addressed by clinical and physical examination and by the individual's ability to conduct the same working activities with respect to the years before PCNSL diagnosis.

Chemotherapy regimens

Patients were treated with different chemotherapy regimens based on HD-MTX according to the period of diagnosis. All these combinations included MTX at 3.5 g/m^2 every 3 weeks. Patients diagnosed between 1991 and 1999 were treated with a combination of HD-MTX, procarbazine, and vincristine (MPV regimen) (8); patients diagnosed between 2000 and 2003 were treated with a combination of HD-MTX, high-dose cytarabine (HD-araC), idarubicin, and thiotepa (MATILDE regimen) (9); patients diagnosed between 2004 and 2007 were treated with HD-MTX alone or with a combination of HD-MTX and HD-araC (10); and patients diagnosed during 2008 were treated with a combination of MTX 3.5 g/m^2 on Day 1, araC 1 g/m^2 twice daily on Days 2 and 3 and thiotepa 30 mg/m^2 on Day 4 (MAT combination; unpublished data).

Radiation fields and doses

Radiation source (photons of 6 MeV) and fractionation (180 cGy per day, 5 weekly fractions) were homogeneous, whereas radiation doses varied in the years. The whole brain was irradiated by two opposite lateral fields including the first two cervical vertebrae and the posterior two thirds of the orbits, which had to be shielded after 30 Gy (after 36 Gy in the case of intraocular involvement). Tumor bed (boost) was irradiated by 2 to 4 isocentric treatment fields based on tumor location, with all portals treated per each RT session. In the case of multifocal lesions, the boost volume included each single lesion. Patients were irradiated to the whole brain with a dose ranging from 30 to 45 Gy and with a tumor bed dose ranging from 36 to 54 Gy.

Treatment planning and image registration

Original treatment planning after a noncontrasted CT scan used for simulation (slice thickness was 3 to 7 mm) and/or profiles obtained at different levels of the radiation field were available in all patients. Both simulation CT scans and profiles were performed with the patient in a supine position; patients were immobilized using a plastic mask and neck support. Every magnetic resonance imaging (MRI) study performed on patients registered for this study at the time of diagnosis, or during treatment and follow-up until failure, was reviewed by one of us (L.S.P.). In patients who has experienced relapse, one neuroradiologist and one radiation oncologist compared the site and volume of relapse with the irradiated volumes using both basal (without delineation) simulation CT or profiles and corresponding magnetic resonance axial image. In patients with a simulation CT scan available, researchers directly delineated the relapse volume (contours) at the consol of treatment planning system (TPS, Cadplan V3.1, Eclipse V7.0, Varian) as determined by lesion detected by contrast-enhanced T1-weighted MR images. Thus, comparison between relapse site and radiation dose distribution was performed.

Statistical considerations

Failure-free survival (FFS) was calculated from the date of diagnosis to relapse, progression, or death, or to the last date of follow-up, and overall survival (OS) was calculated from the date of diagnosis to death or to the last date of follow-up. The FFS and OS curves were generated using the Kaplan-Meier method and compared using the log-rank test. The independent prognostic value of variables (analyzed variables: IELSG score, number of lesions, CSF cytology examination, ocular involvement, chemotherapy regimen, whole-brain radiation dose, and tumor bed dose) was analyzed using the Cox proportional hazard model. Differences in relapse rate and MMSE impairment among therapeutic subgroups were analyzed using the chi-square or Fisher exact test for categoric variables. The comparison between MMSE values before and after therapy was performed by using the Wilcoxon matched pairs test. All statistical tests were two-sided. Analyses were carried out using the Statistica 4.0 statistical package for Windows (Statsoft Inc, 1993, Tulsa, OK 74104, USA).

RESULTS

Study population

Between 1991 and 2008, 99 patients with PCNSL were diagnosed and treated at our institution; 85 were referred to chemotherapy based on HD-MTX as upfront approach. Response after primary chemotherapy was complete in