Primary central nervous system lymphoma (PCNSL) is a relatively rare form of extranodal non-Hodgkin's lymphoma that accounts for approximately 4% of primary central nervous system tumors. Treatment with high-dose methotrexate-based chemotherapeutic regimens have resulted in response rates of 60-70% or higher and long-term survival in 15-30% of patients.1-4 While PCNSL is sensitive to radiation therapy, the duration of response is relatively short, and treatment is associated with delayed neurotoxicity, especially in the elderly.5 Increasingly, there is a debate regarding the value of radiation therapy in the initial treatment of patients with PCNSL. This is reflected in the two ongoing randomized studies of newly diagnosed PCNSL being conducted in the United States. One, sponsored by NRG Oncology, evaluates the value of adding radiation therapy to chemotherapy (NCT01399372). In contrast, a second study, conducted by the Alliance in Clinical Trials in Oncology Cooperative Group, eliminates radiation therapy completely and compares standard chemotherapy alone with chemotherapy followed by autologous stem cell transplantation (NCT01511562). In the subsequent articles, Dr. Lisa DeAngelis from Memorial Sloan Kettering Cancer Center discusses the data supporting a role for radiotherapy for the initial treatment of PCNSL, while Dr. Michael Weller from the University Hospital Zurich provides a counter-argument against the use of radiation therapy.

References
has primary chemorefractory disease. It is time to review this
approach and clarify the potential role of WBRT in patients with
PCNSL.

Historically, WBRT was the sole treatment for the disease we
now recognize as PCNSL. Previously called microglioma or reticu-
lar cell sarcoma, it was only in the 1970’s that the lymphoid
origin of PCNSL was recognized. WBRT was, at the time, the
standard treatment for all primary CNS neoplasms, including ma-
lignant glioma; it was often combined with a boost to areas of
bulky disease. Eventually, several trials showed that limited field
radiation was as effective and less toxic for malignant gliomas,
and WBRT was abandoned. WBRT continued to be used in the
treatment of PCNSL largely because insufficient patient numbers
obviated a comprehensive study. However, the first trial complet-
ed by the Radiation Therapy Oncology Group (RTOG) proved that
WBRT plus a focal boost as sole therapy effectively caused tumor
regression and prolonged survival but only achieved a median
survival of about 1 year, largely because of tumor regrowth. 1
Most importantly, they and others identified that tumor recurred
as frequently within as outside the boosted field, supporting the
need for whole brain but eliminating the need for a boost to areas
of bulky disease. 2, 3 Subsequent studies in Japan demonstrated
that focal RT resulted in increased relapse in regions of the
brain excluded from the RT port, confirming the need for WBRT
in PCNSL when RT is used. 3

Chemotherapy was added to WBRT in the 1980’s when the in-
cidence of PCNSL was increasing. WBRT was retained because it
was the only recognized effective therapeutic modality. However,
it quickly became clear that combination chemotherapy regi-
mens effective for comparable systemic lymphomas (eg, CHOP
[cyclophosphamide/hydroxydaunorubicin/ Oncovin/prednisone])
when added to WBRT did not improve survival over WBRT alone.

High-dose methotrexate was effective in the treatment of the
occasional patient with CNS metastatic disease from lymphoma
or lymphoid leukemias, and when added to WBRT it enhanced
response and prolonged survival in all phase II trials of PCNSL
conducted to date.

Combined modality therapy yielded for the first time pro-
longed disease-free survival, but at the cost of delayed cognitive
impairment that could be progressive and devastating in a pro-
portion of patients. The elderly were most vulnerable, but there
was no safe age threshold. The incidence of neurotoxicity varied
widely depending upon the method of identification, either clini-
cally or with formal psychometric testing, the age distribution of
treated patients, and the length of follow-up; an incidence of
about 30% has been reported in a series of studies. 5, 6 The simple
frequency is often provided as a measure of the toxicity of a given
regimen, but this is an inaccurate means of assessing the true
risk of neurotoxicity from combined modality therapy. A compet-
itive risk analysis adjusts for those patients who relapse. With such
a statistical analysis, it becomes clear that about 24% of patients
develop this complication at 5 years, and the greatest vulnerabil-
ity for neurocognitive impairment occurs within the first 3 years of
diagnosis, plateauing beyond that time. 5 Even more significant is
the high risk of recurrent disease that is twice the risk of neurotox-
icity. Thus, uncontrolled PCNSL is the primary hurdle to both sur-
vival and good quality of life in most PCNSL patients. Prevention of
relapse should be the primary research focus.

So, can WBRT contribute to disease control? There has been
only a single phase III randomized study of patients with
PCNSL, conducted in Germany, in which all patients received high-
dose methotrexate with or without ifosfamide. Those who
achieved a complete response (CR) were then randomized to
receive 45 Gy WBRT or observation; those patients who failed to
achieve a CR were randomized to 45 Gy WBRT or high-dose cytar-
abine. 7 The study was complicated and failed to meet its prede-
termined noninferiority endpoint despite 551 patients being
enrolled. However, the data demonstrated that patients who
received WBRT had a significantly longer progression-free survival
(PFS) of 18 months compared with those who did not receive
WBRT (12 mo). Because there was no difference in overall survival
(OS), many have advocated that WBRT does not add anything
other than toxicity and can be eliminated or replaced with inten-
sified chemotherapy, including stem cell transplant.

Let us examine each issue. First, does WBRT contribute to
survival? The German study failed to demonstrate a survival
benefit; however, there was a 34% noncompliance in the WBRT
arm contrasted with the complete compliance seen in the
chemotherapy-alone arm, making the comparison difficult.
Furthermore, CR patients who received chemotherapy plus
WBRT frequently did not receive salvage treatment, based upon
a median PFS of 36.3 months and a nearly identical median OS
of 38.8 months, compared with patients who received chemo-
therapy alone, where the median PFS was 21.5 months and me-

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2nd, does elimination of WBRT prevent neurotoxicity? It is
well established that WBRT can cause cognitive impairment.
However, there has been a misguided belief that intensive che-
motherapy for PCNSL is free of neurotoxicity. There is mounting
evidence and growing acceptance that systemic chemotherapy
can cause cognitive dysfunction. Such “chemo brain” has been
best studied in patients with breast cancer receiving adjuvant
therapy, but “chemo brain” appears to be caused by a number of
different systemic agents. 10 The mechanisms are unclear
and multifactorial but likely include many of the same mecha-
nisms by which WBRT contributes to cognitive loss, such as
reduced neural stem cell number and function. Studies of cognitive functions after treatment for PCNSL demonstrate that impairment may be more severe when WBRT has been added to systemic chemotherapy, but patients receiving chemotherapy alone often have evidence of impairment as well. Thus, the difference may be more a matter of degree than an all-or-nothing proposition as it has been portrayed.

Furthermore, many of the intensive chemotherapy regimens used to “replace” the anticancer effect of WBRT in PCNSL are themselves quite toxic, causing both acute systemic toxicity and delayed neurotoxicity. Acute toxicities usually include myelosuppression and organ failure, some of which lead to death. The recent report of intensive etoposide and cytarabine for consolidation in PCNSL identified an 81% incidence of grade 4 toxicity and a 4% incidence of death during this part of the regimen. This same regimen used for induction prior to transplant in relapsed PCNSL had a 7% death rate. In the German study, only 79 patients were evaluable for clinically defined neurotoxicity; neurotoxicity was observed in 49% of patients who received WBRT and 26% of those who received chemotherapy alone. Thus, while WBRT increased the risk of cognitive impairment, the proportion of those who developed neurotoxicity from chemotherapy alone was sizable and unexpected. Finally, high-dose chemotherapy with autologous stem cell transplant has been used to “replace” the anticancer effect of WBRT in PCNSL because it reduces relapse and contributes to disease control. It does carry the potential for neurotoxicity, particularly in older patients and when used at full dose. However, if used at a lower dose for patients who have responded to initial chemotherapy, it contributes to a durable remission relatively free of cognitive consequences. WBRT should be an option for patients not enrolled in a clinical trial or who cannot tolerate intensive chemotherapy for consolidation. It is clear that there is no single approach that is best for all patients. Eliminating WBRT from the PCNSL armamentarium would be a mistake and disservice to our patients.

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References


