Treatment of primary CNS lymphoma

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In this issue of Blood, Omuro et al report the results of a phase 2 study for patients with newly diagnosed primary central nervous system lymphoma (PCNSL) using induction immunochemotherapy (rituximab, high-dose methotrexate [MTX], vincristine, procarbazine) followed by a novel consolidation high-dose chemotherapy (thiotepa, busulfan, cyclophosphamide) and autologous stem cell transplantation (HDC-ASCT).1

Although patient numbers are small, the results of the study are remarkable. With a median follow-up of survivors of 45 months, 3-year overall survival (OS) and progression-free survival (PFS) were 81% and 79%, respectively.

Survival of patients with PCNSL given supportive care alone was reported to be 3.3 months.2 As conventional chemotherapy successfully used to treat diffuse large B-cell lymphoma (DLBCL) in sites outside the central nervous system (CNS) proves largely ineffective in PCNSL because drugs do not cross the blood-brain barrier (BBB), the first treatment modality that met with some success was whole-brain radiotherapy (WBRT). However, survival after WBRT was short, usually not exceeding 12 to 18 months, and finally all patients succumbed to their disease. With the availability of leucovorin rescue, high doses of MTX (1.5-8 g/m²) could be administered to patients and achieved concentrations in the brain high enough to effectively destroy tumor cells. Unfortunately, the early studies combining both strategies, WBRT and high-dose MTX, although improving PFS and OS, caused severe neurologic deficits leading to death of some patients otherwise cured from the disease.3 Therefore, a number of studies investigated the efficacy of high-dose MTX alone or in combination with other drugs like ifosfamide, temozolomide, or cytosine-arabinoside (Ara-C) crossing the BBB.4-6 The only randomized study comparing high-dose MTX alone with high-dose MTX plus high-dose Ara-C reported a statistically significant benefit of the combination,4 which therefore is considered current standard therapy by many investigators.

The chemotherapy-only approach caused less neurotoxicity and fairly good tumor control. However, with an OS of 46% at 3 years, results were not completely satisfying. The question of whether WBRT added to the success of therapy if high-dose MTX plus other drugs were used remained unanswered, and the search for better treatment options continued.

Which are the therapeutic elements that contributed to the success of the study by Omuro et al? With a notorious lack of prospective randomized studies in a disease as rare as PCNSL, a strictly scientific answer to the question is not possible, but an educated guess should be allowed. First, some of the recent studies in PCNSL used combinations of drugs (not only MTX) all penetrating into the CNS for a higher number of treatment cycles. This may extend the exposure of lymphoma tissue to cytotoxic drugs, which seems to make sense as this and other studies report ongoing tumor responses after 4 or 5 cycles of therapy. Second, the administration of rituximab in higher-than-standard doses (500 mg/m²) may have contributed to the effectiveness of induction therapy. Although it is clear that rituximab administered IV virtually does not cross the BBB of healthy individuals, the situation is different in patients with brain lymphoma. We and others have seen responses to rituximab monotherapy in patients with PCNSL or secondary involvement of the CNS by DLBCL. Third, although the concept of consolidation therapy is not new, the introduction of HDC including drugs like thiotepa, busulfan, and carmustine, and thereby achieving very high concentrations of effective drugs in the brain, certainly was a major step forward. The importance of HDC-ASCT is highlighted by reports showing that the complete response and overall response rates after HDC-ASCT dramatically improved when compared with the responses to the preceding conventional chemotherapy.7

Omuro et al8 are to be congratulated on performing this study not only because of the high efficacy of their strategy but also because they included a prospective assessment of neurocognitive function into their study. It has been a major problem of many studies in PCNSL that deterioration in neurologic function was reported, but it was not clear how this was objectively measured and how the results of one study would compare with those reported by others. The neuropsychological tests, quality-of-life assessments, and radiographic evaluation of neurotoxicity delivered with this study show that PCNSL can cause impairment of cognitive functions by itself before any treatment is given. The multiple tests chosen by the authors to document neurologic function demonstrate an improvement of deficits over time and a lack of severe neurologic deficits elicited by therapy itself. Of course, the observation period of surviving patients is not long enough to preclude long-term sequelae of therapy. Therefore, further follow-up is definitely warranted.

In summary, during a time period of no longer than 25 years PCNSL has turned from a unanimously deadly disease to a highly curable disorder. To further improve the situation, a better understanding of the molecular background of PCNSL9 may help to integrate some of the new orally available small molecules into our treatment strategies. This might not only further improve treatment results but also allow treatment of older and frail patients and spare all patients the acute and long-term toxicities of current radio- and chemotherapy regimens.

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Malignant TOXication of T cells

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In this issue of Blood, Huang et al show that aberrant expression of TOX plays a central role in malignant survival, proliferation, and tumor formation in cutaneous T-cell lymphoma (CTCL).1

CTCL is a relatively rare and mysterious T-cell malignancy of unknown etiology. The key feature is clonal expansion of malignant T cells, but the pathogenesis is far from understood. The big question is what drives transformation from an indolent skin condition with a good prognosis and a normal life expectancy to a highly aggressive cancer with a poor prognosis. Here, Huang et al1 show that aberrant expression of thymocyte selection-associated high-mobility group (HMG) box gene TOX is associated with increased disease-specific mortality in patients with Sézary syndrome, a leukemic variant of CTCL. Importantly, TOX drives mitogenesis and survival of malignant T cells in vitro and tumor formation in vivo. The effect on cell cycle progression is notably mediated through a TOX-dependent repression of the 2 cyclin-dependent kinase inhibitors CDKN1B and CDKN1C, providing the first evidence of a direct link between TOX and these cell cycle regulators.1

TOX is a nuclear factor which is expressed in the thymus in a stage-specific and regulated manner and believed to play an important role during development of double-positive thymocytes.2 T-cell receptor (TCR)-mediated signaling drives TOX expression during positive selection, and mice deficient in TOX reveal a requirement for this factor in the development of all CD4+ T lineage cells, including conventional CD4+ T cells, FoxP3+ regulatory T cells, and natural killer T cells.3 Yet, the upregulation of TOX is transient and associated with thymic development but is not seen in mature, naive CD4+ T cells.2 Malignant T cells in Sézary syndrome patients resemble healthy mature CD4+ cells and display a phenotype similar to that of central memory CD4+ T cells.4 The discovery by Huang et al1 of an ectopic expression and function of a thymic transcription factor (TOX) in malignant T cells strongly indicates that these cells are distinctly different from their healthy counterparts and have similarities with immature thymocytes. An aberrant TOX expression is not a unique feature of Sézary syndrome T cells. Patients with the more common variant of CTCL, mycosis fungoides, also display ectopic expression of TOX by malignant T cells. Interestingly, they also display aberrant expression of other thymic genes such as the B lymphoid kinase (BLK) and cancer-testis genes, which are not expressed in mature peripheral and skin resident T cells.5,6 In concert with the present study by Huang et al,1 these findings could suggest that malignant T cells either arise from a transformed thymic stem cell or become deregulated, “reopening” a thymic expression program (see figure). The fact that malignant T cells usually display a fully completed TCR rearrangement, a functional TCR CD3 complex (at least in the initial stages of the disease), and a phenotype similar to that of a mature T cell argues against an early thymic stem cell origin. Therefore, I propose that the aberrant expression of thymic and stem cell genes is a result of a dedifferentiation, leading to re-expression of TOX, BLK, and other developmental genes in the malignant T cell or its malignant precursor in the

A proposed model of malignant dedifferentiation and TOX expression in CTCL. TOX and BLK become upregulated during thymic development of CD4+ T cells (left). In contrast, mature peripheral CD4+ T cells do not upregulate TOX on TCR stimulation and do not express BLK (middle). TOX- and BLK-positive malignant T-cell clones arise from a deranged thymic stem cell (dashed arrow) or as a result of TOX-dependent and/or TOX-independent dedifferentiation of malignant T cells or a precursor T cell (solid arrow). Dedifferentiation of the malignant T cell (or a precursor T cell) drives deregulated expression of transcription factors (including TOX), Scr kinases (including BLK), cytokines, and lymphangiogenic factor (right), leading to progressive disease and a mixed phenotype mimicking Th2, Th17, Th22, central memory/resident memory T cells (Tcm/Treg), and LTi cells (right). Professional illustration by Luk Cox, Somersault 18:24.
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