inside blood commentary

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Donadieu et al, page 1415

Risk organ + LCH gets the one-two punch?

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In this issue of *Blood*, Donadieu et al[1] present what may be the most encouraging data to date on a group of patients with Langerhans cell histiocytosis (LCH), which historically has poor disease-free survival and poor overall survival.

Since the beginning of the Histiocyte Society, when a small group of clinicians and scientists gathered in Philadelphia almost 30 years ago,[2] investigators have been trying to understand this disease and its treatment and outcomes better through collaborative studies. During the past 3 decades, this small group of investigators has grown and reached out to an international contingent that recognized that any changes in the diagnosis and treatment of patients with such a rare disorder as LCH would require international collaboration. The group expanded in size and commitment, assembling clinical trials and gathering data on outcomes and late effects, and developing treatment algorithms. Over the next 20 years, several studies were completed that highlighted that children with disease involving the bone marrow, spleen, and liver (ie, risk organs) have a poor prognosis; children who failed to respond to induction therapy had a poor survival; children with disease affecting the facial bones would be at risk for a unique group of late effects including diabetes insipidus; and even with continued attempts to increase disease control, some children would inevitably develop recurrent disease.[3-5] The group with the worst prognosis and survival throughout these clinical trials has continued to consist of children with disease involving the bone marrow, liver, or spleen who did not respond to routine induction therapy or had a reactivation of their disease involving one of these high-risk organs. This group of patients has an overall 2-year survival rate of <30%.[6] There have been a small series of reports suggesting that more aggressive therapy mimicking acute myeloid leukemia therapy may have an impact on this disease.[7,8] Bernard et al took this concept one step further and reported their results of a pilot study of 10 patients treated in France with the combination of high-dose 2-cladribine and cytosine arabinoside.[9] The data were encouraging, and a phase 2 trial using the resources of the Histiocyte Society was initiated. The results of that study are reported in this issue. The intent of the study was to be an international collaboration with strict inclusion criteria and a well-defined treatment plan. The study was only able to accrue patients in Europe. A total of 27 patients were enrolled over the 5-year period. The primary end point was disease status after 2 courses of the 2-drug therapy.

LCH disease status has been reported since that initial meeting using a simple schema of nonactive disease, active disease better, active disease stable, and active disease worse.[10] The problem for such an evaluation system was that LCH is not a simple disorder involving one organ or one site of one organ. The need for a system that might aid clinicians to grasp a more fluid and flexible disease evaluation system became apparent. Donadieu et al used a disease activity score (DAS) in this study to follow these patients. It is important to note that the primary objectives of the response to 2 courses of therapy and length of time to achieve complete remission were based on the standard LCH disease activity system. The investigators report that the use of this DAS will aid clinicians in better understanding the disease response or lack thereof in future clinical trials. The bottom line is that, of the 27 patients reported, the investigators report an overall response rate of 92% and a long-term survival rate of 85%. However, there is a caveat whenever a highly toxic regimen is used, and the investigators reported these acute and late effects.

For the first time since the founding of the Histiocyte Society, a regimen used in a multi-institutional trial demonstrates that children with disease of the bone marrow, liver, or spleen who do not respond to standard induction therapy can be treated with intensive chemotherapy. So what is next?

The Histiocyte Society has launched the LCH-IV study, with one of the strata addressing similar patients: risk organ–positive patients who do not respond to up-front induction. The treatment plan is a slight modification of the reported salvage therapy in an attempt to decrease toxicity yet maintain the improved overall survival seen in this phase 2 trial. Time, perseverance, and collaboration highlight the slow and steady progress in the treatment of this rare disease. Only time and collaboration will determine whether this type of therapy will have the long-lasting impact suggested by the results of Donadieu et al.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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Comment on Yang et al, page 1424

Nasal NK/T-cell lymphoma: RT, CT, or both

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In this issue of *Blood*, Yang et al have proposed that for early-stage nasal type natural killer (NK)/T-cell lymphoma, combined radiotherapy (RT), and chemotherapy (CT) improve survival, but CT can be safely omitted in certain low-risk patients treated with RT.[1]

NK/T-cell lymphoma, nasal type, is a rare malignancy with a geographical predilection for Asian and South American populations.[2] It is uniformly associated with clonal episomal Epstein-Barr virus (EBV) infection in the lymphoma cells.[2] Early-stage nasal NK/T-cell lymphomas refer to lymphomas affecting the nose, nasopharynx, the upper aerodigestive tract, and the draining lymph nodes without distant tissue involvement (Ann Arbor stages I and II). RT has traditionally been considered an important treatment component because NK/T-cell lymphomas are radiosensitive. RT alone in early-stage patients resulted in overall response rates ranging from 80% to 100% and complete response rates of 50% to 100%.[2] However, systemic relapses occurred in up to 40% of patients, indicating the presence of occult systemic metastases in apparently early-stage diseases. The belief that additional CT might not be beneficial was based on older studies using anthracycline-containing regimens, which were largely ineffective for NK/T-cell lymphomas because neoplastic cells express high levels of P-glycoprotein.[2]

Yang and colleagues studied a large cohort of nasal NK/T-cell lymphomas and examined the relative roles of RT, CT, and their combinations in early-stage patients.[1] They showed that CT alone was inferior to RT or combined RT and CT. They further divided their patients into different risk groups according to 5 clinicopathologic parameters: age >60 years, performance status Eastern Cooperative Oncology Group ≥2, stage II disease, elevated lactate dehydrogenase level, and presence of primary tumor invasion into surrounding tissues. For the low-risk group (having none of these factors), the 5-year progression-free survival was comparable for patients treated with RT (79.2%), RT followed by CT (81.6%), and CT followed by RT (71.5%). Similarly, the 5-year overall survival was also comparable for RT (88.8%), RT followed by CT (86.9%), and CT followed by RT (86.3%). Interestingly, the treatment outcome of these low-risk patients was also comparable with that of unselected patients treated with concurrent CT and RT in previous prospective clinical trials.[3,4] Yang et al therefore propose that, in low-risk patients, the addition of CT to RT does not improve survival. However, it is noteworthy that the relapse rate for low-risk patients receiving RT alone was still significant at 18.8% in their study,[1] suggesting that some of these patients did not really have "early-stage" disease.

NK/T-cell lymphoma is curable in a significant proportion of patients. The identification of high-risk patients who could benefit from additional or novel therapy may further improve outcome. Just like other aggressive lymphomas, prognostication models have moved beyond simple clinicopathologic parameters. Circulating EBV DNA,[5] positron emission tomography/computed tomography (PET/CT) scan, and combined evaluation of EBV DNA and PET/CT scan[6] very accurately determine risk groups and predict outcome in NK/T-cell lymphomas. Ongoing efforts are devoted to integrating these investigations

Treatment outcome of early-stage NK/T-cell lymphoma using combined RT and CT in selected studies

Treatment	No. patients	ORR, %	CR, %	OS	PFS	Reference
RT → CHOP	172	93.3	82.2	3 y: ~80%	NA	1
RT → L-asparaginase/gem-based CT	37	93.3	82.2	3 y: ~80%	NA	
CHOP → RT	523	61.3	25.1	3 y: ~70%	NA	
L-asparaginase/gem-based CT → RT	118	77.9	31.6	3 y: ~70%	NA	
SMILE + sandwich RT	29	86	69	NA	NA	7
LVP + sandwich RT	26	92	42	2 y: 89%	2 y: 81%	8
GELOX + sandwich RT	27	93	56	2 y: 86%	2 y: 86%	9

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR, complete response rate after initial RT or CT; GELOX, gemcitabine, L-asparaginase, and oxaliplatin; gem, gemcitabine; LVP, L-asparaginase, vincristine, and prednisolone; ORR: overall response rate after initial RT or CT; OS, overall survival; PFS, progression-free survival; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide.