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CLINICAL TRIALS AND OBSERVATIONS

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.

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with clinicopathologic parameters for even better risk stratification.

Although RT is conventionally used in early-stage cases, it is not employed in advanced-stage patients. With current L-asparaginase–containing regimens, up to 50% of advanced-stage patients who have not received RT achieve durable remission,[7] clearly showing that RT is not mandatory for NK/T-cell lymphomas.

CT, however, is increasingly recognized as an indispensable treatment component. The beneficial effect of CT is also shown by Yang et al.[1] In high-risk patients, the 5-year overall survival for RT followed by CT was 72.8%, compared with 57.9% for RT alone. Yang et al reported that CT followed by RT gave poor results. This observation is undoubtedly from their upfront use of ineffective anthracycline-containing regimens. Furthermore, their results of L-asparaginase–containing regimens were surprisingly worse than other studies for early-stage NK/T-cell lymphomas (see table). This may be related to a small number of patients in their study who received heterogeneous L-asparaginase–containing regimens. In fact, prospective clinical trials have shown that, with effective CT, concurrent RT/CT or CT followed by RT gave very comparable results.[3,4,7-9] Therefore, the sequence of RT and CT may not be critical.

Although physicians will continue to give RT to early-stage patients, the high systemic failure rates of RT alone, even for low-risk patients in the study by Yang et al, mean that optimal schedules of additional CT to eradicate occult systemic spread should be determined. Intriguingly, it may even be possible to define in the future if RT can be safely omitted in specific groups of early-stage NK/T-cell lymphomas because short- and long-term toxicities of RT are considerable and may have permanent impacts on quality of life, particularly for elderly patients.

The results of Yang et al, which rely on simple clinicopathologic parameters to determine whether early-stage nasal NK/T-cell lymphoma patients may receive RT alone, are useful for resource-limited centers where more expensive investigations are not available and complicated CT regimens are not feasible.[10] In better-equipped centers, PET/CT scan and EBV DNA, neither used by Yang et al, should be employed for more exact staging and prognostication. These approaches more precisely identify patients with genuine early-stage limited disease, enabling clinical studies to establish the best modality of treatment that will lead to durable remissions in these patients.

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● ● ● LYMPHOID NEOPLASIA

Comment on Leone et al, page 1443

Myeloma escape from immunity: an "inside" job

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In this issue of *Blood*, Leone et al describe a novel mechanism mediated by bone marrow dendritic cells (DCs) that impairs T-cell recognition and killing of myeloma cells.[1]

A small but growing population of patients who remain in complete remission and are progression free at 10 years after diagnosis of multiple myeloma (MM) is emerging as a result of the use of the "total therapy" concept pioneered by Barlogie et al.[2] Total therapy uses highly active myeloma first-line therapies followed by 1 or 2 autologous stem cell transplantations (SCTs) and consolidation/maintenance therapy. Still only about 30% of MM patients are cured according to these criteria, and a much smaller fraction of patients with high-risk disease reach these milestones. Initial enthusiasm for an immunotherapeutic approach to MM based on evidence for a graft-versus-myeloma effect in the setting of allogeneic SCT has been tempered by the high risks of morbidity and mortality from graft-versus-host disease and by the higher-than-expected rate of relapse.[3,4] Mechanisms of immune evasion by MM cells are variable but are likely to include reduced expression of HLA molecules, reduced expression of tumor antigen peptides, enhanced expression of inhibitory ligands such as programmed cell death ligand 1 (PD-L1) and PD-L2, and recruitment of counterregulatory cells such as T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs).

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