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TP53 binding domain mutations are bad news in Burkitt lymphoma

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Disclosures

Dr. Cairo currently serves as a consultant for Jazz Pharmaceuticals and Abbvie and is on the Speakers Bureau for Jazz Pharmaceuticals and Sobi.

Martire et al., has elegantly demonstrated that besides the use of rituximab in chemoimmunotherapy backbone regimens, that minimal disseminated disease (MDD) at diagnosis and TP53 binding domain mutations are associated with a significantly decreased progression free survival (PFS) in children, adolescents and young adults (CAYA) with Burkitt lymphoma (BL).(1) We and others have previously demonstrated that the addition of rituximab to CAYA with advanced stage BL significantly increases event free survival (EFS).(2-5) Our group previously demonstrated that 13q14.3 deletions and potentially deletion of Deleted in Lymphocytic Leukemia 1 (DLEU1) is associated with a significantly decreased EFS in CAYA with BL.(6, 7) In this recent study by Martire et al., and her team from the University of Padova, they analyzed 214 cases of pediatric BL between 1999-2022, in which there was both tumor

tissue and bone marrow and/or peripheral blood at diagnosis to perform TP53 DNA binding domain mutation studies, utilizing Sanger sequencing of hot spot exons 5 to 8 and molecular disease dissemination.(1) This group demonstrated that approximately 40% of patients possessed a TP53 DNA binding mutation, which following a multivariate analysis, was specifically associated with a significantly decreased 2yr PFS (91±3% vs 76±5% [P < 0.005]). When combining TP53 DNA binding mutation plus the presence of MDD at diagnosis, the 2yr PFS was significantly decreased compared to the subset without TP53 binding domain mutations and MDD (92±3% vs 70±7% [P < 0.01]). This same subgroup possessing both MDD and TP53 binding domain mutations was also associated with a significantly decreased 2yr overall survival (OS). Furthermore, in the subgroup with a TP53 binding domain mutation and MDD but not receiving rituximab, the 2yr PFS was significantly decreased compared to those without a TP53 DNA binding mutation, nor MDD and without rituximab administration (88±4% vs 75±6% [P < 0.02]).

TP53 is a gene located on chromosome 17 (17p13.1) and encodes for a 53-kDa protein. The gene has 11 exons and codes for an mRNA of 2.5Kb and a protein of approximately 393 amino acids. TP53 is a master negative regulator of cell proliferation and a positive regulator of cell apoptosis in response to DNA damaging agents. In fact, TP53 is the most commonly mutated gene in human cancer, both inherited and sporadic subtypes. Importantly, Li-Fraumeni syndrome is a multicancer predisposition syndrome that is characterized by constitutional TP53 mutations.(8) TP53 is a nuclear phosphoprotein and has a sequence-specific DNA binding activity and functions both as a transcriptional activator and repressor and in part regulates whether cells undergo cell cycle arrest and repair, or enters into repetitive senescence. The loss of TP53 function is associated with significantly decreased outcomes in patients with a number of

malignancies, including lung, breast, colorectal, melanoma, and some hematopoietic cancers. Mutations in TP53 in tumors compromises its role in tumor cell surveillance and triage, facilitating mutated tumor cells to survive and generate new and more malignant subtypes. TP53 mutations in numerous cancers have resulted in the labeling of this gene as a classical tumor suppressor gene.(9)

In this study Martire et al. also demonstrated that biallelic abnormalities were significantly associated with a decreased 2yr PFS and OS compared to monoallelic abnormalities. While the types of mutations were subdivided by both mutations in exons 5-8 and by the following subtypes of mutations: missense mutations, nonsense mutations, inframe deletions, frame shift and single nucleotide variant. However, the numbers were quite small to determine whether specific mutations and/or exon location were more prognostic. In the multivariate analysis including age, gender, bone marrow, central nervous system, risk group, stage, MDD and use of rituximab were utilized. However, only TP53 DNA binding mutations and treatment with rituximab were significant variables ($P < 0.024$ or $P < 0.0318$), respectively. Elevated lactate dehydrogenase, a previous well know independent prognostic factor, however, was not included in this recent multivariate analysis.(2-4)

This important contribution to the field expands our existing knowledge in the heterogeneity of the genomic makeup of CAYA with BL. These TP53 DNA binding domain mutations, as identified in this study, along with the 13q14.1 (DLEU1) deletions and the MYC Burkitt-like lymphoma (BLL) associated with 11q aberrations (mbBLL, 11q) all are subsets with alterations in the genomic landscape of CAYA with BL that are derived from germinal center centroblasts (Figure 1). The former two, TP53 DNA binding mutations and 13q14.3 deletions are associated with an inferior prognosis, whereas the latter mbBLL-11q is associated with a significant

improvement in the prognosis of CAYA with BL.(1, 6, 7, 10) Hopefully, future investigations will elucidate the exact mechanisms associated with either decreased or increased survival with each of these genomic abnormalities in CAYA with BL. This contribution by Martire et al. will facilitate our increased understanding of both the genetic heterogeneity of BL in CAYA and the importance of targeted antibody immune based therapy to overcome and/or circumvent previous known risk factors in those subtypes previously associated with an inferior outcome.

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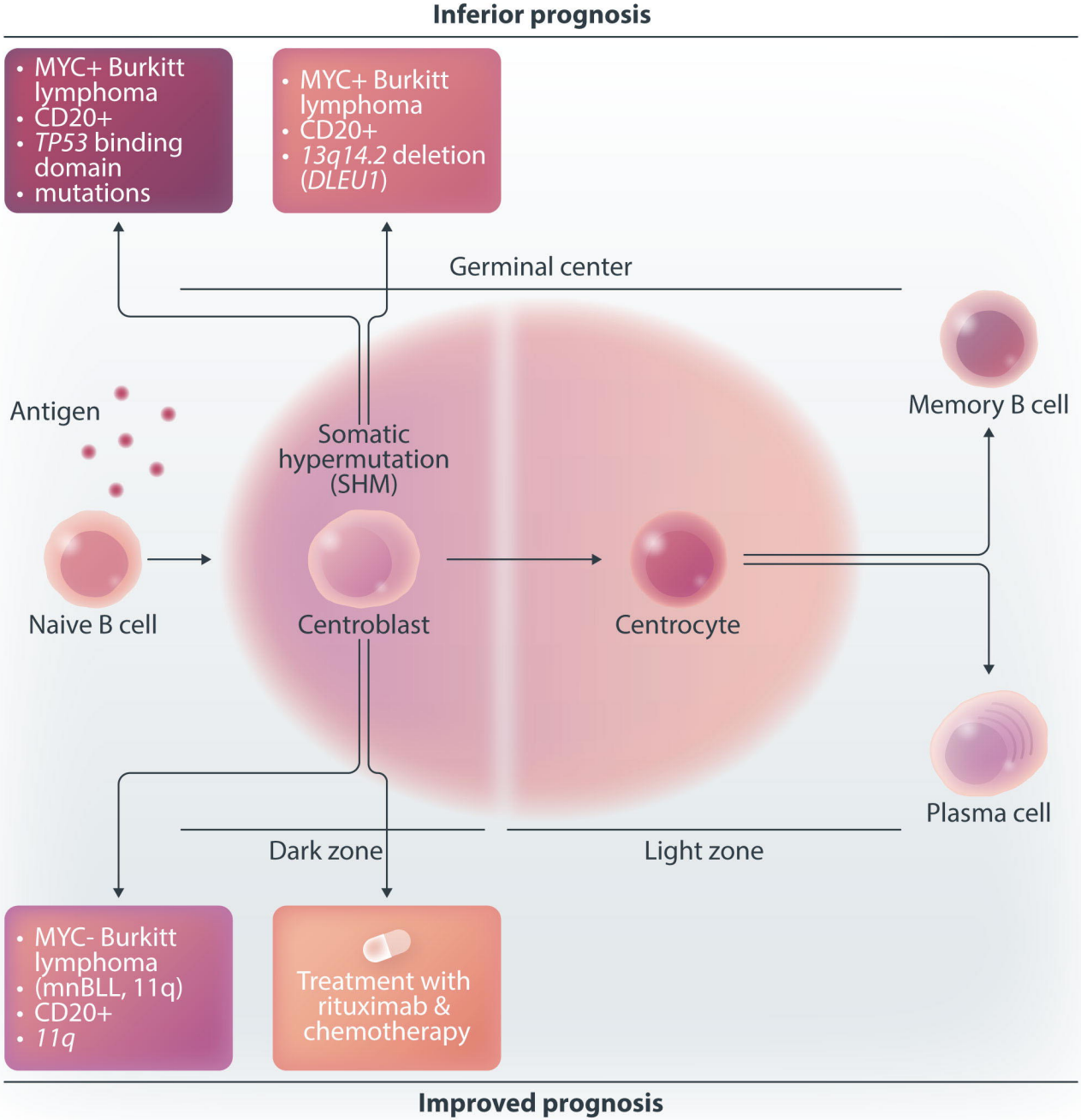
Figure Legends

Figure 1. Genomic changes associated with improved and inferior outcome in subsets of children, adolescents and young adults with Burkitt lymphoma.


Inferior prognosis
• MYC+ Burkitt lymphoma
• CD20+
• TP53 binding domain
• mutations
• MYC+ Burkitt lymphoma
• CD20+
• 13q14.2 deletion (DLEU1)
Germinal center
Antigen
Somatic hypermutation (SHM)
Memory B cell
Naive B cell
Centroblast
Centrocyte
Plasma cell
Dark zone
Light zone
• MYC- Burkitt lymphoma
• (mnBLL, 11q)
• CD20+
• 11q
Treatment with rituximab & chemotherapy
Improved prognosis