Richter syndrome (RS) is defined as the molecular and genetic transformation of chronic lymphocytic leukemia (CLL) into one of two morphology types based on histology. It has an annual occurrence of 2% to 10% in CLL patients (Rossi et al., 2018; Tadmor & Levy, 2021). The more common is that of an aggressive lymphoma, diffuse large B-cell lymphoma (DLBCL-type RS), or rarely evolution into Hodgkin lymphoma.

Suspicion for RS is based on clinical signs and symptoms such as fever, rapid physical deterioration, thrombocytopenia, excessive rise in lactate dehydrogenase, increasing bulky lymphadenopathy or splenomegaly, and/or hypercalcemia (Rossi et al., 2018). Those evolving to DLBCL-type RS have a poor prognosis, therefore representing the greatest unmet need in CLL therapy (Rossi et al., 2018; Tadmor & Levy, 2021).

Richter syndrome that is clonally unrelated to the paired CLL is clinically and biologically distinct from clonally related RS in terms of superior survival, with a median of 62 months vs. 8 to 16 months, respectively, along with lower prevalence of TP53 mutations (Abrisqueta et al., 2017; Rossi et al., 2018). These data highlight the genetic heterogeneity of RS. In an effort to devise effective treatment modalities elucidating the mechanisms whereby mutations in TP53, CDKN2A, MYC, B-cell receptor (BCR) signaling dysregulation, and NOTCH1 signaling lead to the constellation of evasion from apoptosis, chemorefractoriness and rapid proliferation are under investigation (Tadmor & Levy, 2021). Other biological prognosticators for predication of RS include unmutated IGHV and stereotyped BCR particularly if combined with IGHV4-39 usage (Rossi et al., 2018; Tadmor & Levy, 2021).

**Key Points**
- Richter syndrome has a very poor prognosis, representing a great unmet need in CLL therapy.
- It is necessary to elucidate roles of mutations such as TP53, CDKN2A, MYC, BCR signaling dysregulation, and NOTCH1 signaling to develop effective treatment modalities.
- It is important for advanced practitioners to be cognizant of prognostic markers and mutations conferring high risk for RS.

**NOVEL AGENTS**

Historically, chemoimmunotherapy is given for RS; however, TP53 mutations confer chemorefractoriness, with progression-free survival (PFS) rates of approximately 6 months and median overall survival (OS) of 8 to 10 months (Rossi et al., 2018; Tadmor & Levy, 2021). Novel agents for high-risk CLL capable of overcoming such signaling aberrations have paved the way for clinical trials investigating their efficacy for RS treatment.

Venetoclax (Venclexta), a selective inhibitor of the anti-apoptotic protein B cell lymphoma,
combined with DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin hydrochloride) with rituximab across non-Hodgkin lymphoma types was investigated in a phase II trial, with the RS patients showing an overall response rate (ORR) of 76%, complete response (CR) rate of 48%, and median PFS of 16.3 months, which is improved from historical controls (Davids et al., 2020). Signaling through BCR is a known mechanism for Richter cell survival as evidenced by a majority of RS having a subset 8 configuration of the BCR, which drives strong pathway signaling (Gounari et al., 2015).

Acalabrutinib (Calquence), a Bruton tyrosine kinase inhibitor (BTKi), was explored in the phase I/II ACE-CL-001 study, with 29 RS patients with an ORR of 38%, median duration of response (DOR) of 5.2 months, and median PFS of 2.1 months (Hillmen et al., 2016).

BTK and PLCG2 mutations that confer BTKi resistance are present in ~40% of RS patients receiving prior ibrutinib (Imbruvica), a BTKi (Jurczak et al., 2021; Rossi et al., 2018; Tadmor & Levy, 2021). Therefore, pirtobrutinib, a non-covalent BTKi, was examined in a small trial of nine patients showing an initial ORR of 75% (Jurczak et al., 2021). While follow-up is short, we await results of the ongoing phase I/II BRUIN study.

Programmed cell death protein 1 (PD-1) is highly expressed in RS with inhibition of immune surveillance; therefore, studies have looked at pembrolizumab (Keytruda), a PD-1 blocking antibody, and nivolumab plus ibrutinib (Ding et al., 2017; Jain et al., 2016). Both checkpoint inhibitors show meaningful ORR rates, with pembrolizumab at 44% and nivolumab + ibrutinib at 43% in treating RS (Ding et al., 2017; Jain et al., 2016). Future studies are exploring CAR T and bispecific antibodies that attach to both CD20 on B cells and CD3 on T cells (Holstein & Lunning, 2019). Early data with aggressive lymphomas is yielding encouraging results.

The Advanced Practitioner Perspective

The future for DLBCL-type RS management is promising with novel combination regimens, as the disease heterogeneity makes a standardized approach difficult. Ongoing research aimed at elucidating the roles specific mutations impart to RS will enhance our biological understanding of the disease in an effort to develop beneficial therapies. Advanced practitioners should be cognizant of these research efforts as well as ongoing clinical trials utilizing novel agents poised to overcome such genomic complexity and improve patient outcomes.

Disclosure

Dr. Nodzon has served on the speakers bureaus for AbbVie and Genentech and as a consultant for AbbVie, AstraZeneca, Genentech, Pharmacia, and Takeda.

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