Richter's Syndrome: CLL Taking a Turn for the Worse

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Early results suggest that the new targeted therapies for CLL may have a profound impact on survival—and thus on the incidence of Richter's transformation. It will therefore become increasingly important to study Richter's transformation more assiduously, to diagnose it sooner, and to develop strategies to treat this extremely challenging entity.

Jain and O'Brien's review summarizes the evidence for the diagnosis and management of Richter's transformation (RT)[1,2] and introduces several challenges posed by a transformation to aggressive lymphoma in patients with chronic lymphocytic leukemia (CLL).

RT is one of the most feared developments in CLL. In its “true” form, RT has little effective therapy and a very poor outcome. Most trials for CLL, including those that involve the novel targeted therapies that promise to revolutionize the treatment of CLL, have an exclusion criteria for RT. At the same time, the advent of more effective therapies for CLL is altering the expectations of patients and their families regarding the prospect of long-term disease control and possibly even cure. This makes the development of RT even more devastating.

To make matters worse, the problem of RT is likely to become more frequent. The longer a patient survives with CLL, and the more lines of therapy he or she receives, the greater the probability that RT will develop.[3] The most effective therapy for CLL is chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab (Rituxan) (FCR). Use of FCR has increased the median overall survival significantly, meaning that patients are more likely to transform. The advent of targeted therapies, such as the Bruton's tyrosine kinase (Btk) inhibitor, ibrutinib, or the phosphatidylinositol-3 kinase δ inhibitor, GS-1101, promise to extend survival even further.[4,5] However, these agents do not prevent RT and therefore are likely to increase the incidence of RT due to prolonged survival.

It is therefore important that clinicians maintain a high level of suspicion for transformation in CLL and investigate to exclude it. However, as the Jain and O'Brien review highlights, this task is not without pitfalls. The diagnosis of RT is not always straightforward. It may be suspected if a patient has one lymph node area that is enlarging out of keeping with the rest of his or her disease, or if one area does not respond to therapy for CLL while the remainder of the disease responds well. This sort of disproportionate enlargement of one node might also indicate which lymph node mass should be biopsied—but not infrequently one part of the same mass does not. There are emerging data that the use of positron emission tomography—computed tomography (PET-CT) scanning might help to exclude RT, or at least might indicate which lymph node should be biopsied. It must be emphasized, however, that it is essential to prove transformation by an appropriate biopsy, as this will guide therapy.

It is important that clear diagnostic criteria be established and that they be applied rigorously so that a baseline rate of RT might be established; this will make it possible for any changes resulting from changing therapeutic patterns to be recorded. For example, it is entirely possible that EBV-driven lymphoproliferative disorder, masquerading as true RT, will become more prevalent (or less so), and such a development will have an impact on the treatments used for the transformed disease.

Not only is RT frequently a difficult diagnosis to establish but it also presents a huge therapeutic challenge. For example, the standard therapies used in CLL, such as fludarabine-based chemo-immunotherapy, are not appropriate or effective in RT. There is no standard therapy for RT, with most clinicians falling back on conventional chemotherapy for diffuse large B-cell lymphoma, namely CHOP-R (cyclophosphamide, doxorubicin, vincristine, and prednisone, plus rituximab), but this has a much worse outcome in RT than in de novo disease. Therefore, achieving a complete remission is difficult, and even if remission is achieved, most patients will relapse. This has led to the use of allogeneic stem-cell transplantation for patients achieving complete remissions, although only a small minority of patients will achieve an adequate remission and be fit enough to proceed to transplant.[6,7] It certainly seems clear that patients with RT who do not achieve a complete remission have a much worse outcome post-transplant (either autologous or allogeneic) and that
transplantation possibly should not be considered as a standard therapy. In addition, although the outlook for patients transplanted in complete remission looks much better, these data are suspect, since these are only the patients who have responded well to treatment for their RT and may have done well anyhow.

The classification of RT is important and will influence the choice of therapy. The classic description of a clonal evolution from the CLL clone itself carries a very poor prognosis, whereas with the increasing use of immune-suppressive treatments for CLL, such as alemtuzumab (Campath)-based therapies, Epstein-Barr virus (EBV)-driven transformation that is not clonally related to the patient's CLL is more frequently being diagnosed. EBV-transformed disease is more analogous to post-transplant lymphoproliferative disorder and appears to have a significantly better prognosis than true RT.[8] In addition, a small proportion of aggressive transformations of CLL are Hodgkin's disease, and these are more usually treated with Hodgkin's-like therapy.

In summary, Jain and O'Brien's review of Richter's transformation is timely, as early results suggest that the new targeted therapies for CLL may have a profound impact on survival—and thus on the incidence of RT. It will therefore become increasingly important to study RT more assiduously, to diagnose it sooner, and to develop strategies to treat this extremely challenging entity.

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References:

REFERENCES

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