PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

LYMPHOMA

Richter's transformation
(Diffuse large B-cell lymphoma)

Site Group: Lymphoma

Date guideline created: December 2023

1. Introduction

Richter's transformation (RT) is a term used to refer to aggressive lymphoma transformation in patients with chronic lymphocytic leukemia (CLL). While the most common transformation is to diffuse large B-cell lymphoma (DLBCL), a proportion of cases transform to Hodgkin lymphoma. Only DLBCL-RT management is described below.

RT is clinically suspected when patients with CLL develop rapidly progressive lymphadenopathy and/or constitutional symptoms. The clinical picture of RT may be further supported when laboratory abnormalities such as elevated LDH or hypercalcemia exist. PET-CT may be useful to determine location for targeted biopsy. PET-CT may also be useful in its negative predictive value (NPV), as low uptake (SUVmax <5) has a high NPV in ruling out Richter's transformation. On the other hand, high SUVmax does not have high specificity or positive predictive value in diagnosing RT, illustrating the importance of biopsy to confirm clinical or radiographic suspicion of RT.

2. Prevention

Prevention strategies are not currently available for Richter's transformation. The reported incidence of RT varies depending on data sources, but a Danish population based study of 3771 patients with CLL found a 3% incidence of RT during a median follow up period of 4.3 years. Risk factors are not well defined, but reported factors include advanced stage, unmutated IGHV, IGHV4-39 rearrangement with stereotyped HCDR3 (IGHV subset 8), NOTCH1 mutations, and TP53 aberrations.

3. Screening and Early Detection

Screening and early detection do not play a role in the diagnosis and management of RT. Patients should be counselled on signs and symptoms of RT, especially those at increased risk.

4. Diagnosis

The diagnosis of Richter's transformation is dependent on immunophenotypic findings and histologic assessment of a surgically acquired core or excisional biopsy of an involved lymph node or other extra-nodal tissue, to ensure adequate evaluation based on morphology, immunohistochemistry, flow cytometry, FISH, and molecular testing for accurate sub-typing. Bone marrow aspiration and biopsy are recommended for staging, given that predictive value of PET to assess for bone marrow involvement in patients with RT is unclear.

5. Pathology

Patients are treated based on a diagnosis conforming to those described according to the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HEAM5) and/or the International Consensus Classification (ICC). Expert hematopathology review is critical in the diagnosis of DLBCL-RT. The immunophenotype is determined either immunohistochemistry on tissue with a panel consisting of CD5, CD20, CD23, CD30, BCL2, BCL6, PAX5, PD1, MUM1, MYC, EBER(ISH), TP53, MIB1. In addition, CD3 is added to the panel for detection of stromal T

cells.

DLBCL-RT can be subdivided into clonally related to underlying CLL (60-80% of cases) and clonally unrelated (20-40% of cases). Factors considered for pathology review include clonality assessment (feasibility to be determined by pathologist), TP53 mutational testing, immunohistochemistry (IHC) for PD1. Findings diagnostic of a clonal relationship include: (1) identical IGHV sequence of separate Richter's specimen and CLL specimen. Findings that increase the likelihood but are not diagnostic of a clonal relationship of the Richter's clone to the CLL include (1) TP53 mutation testing positive; (2) IHC positive for PD1.

6. Management

Pre-treatment evaluation and staging:

- Full history and physical examination including performance status
- CBC, albumin, LDH, liver testing (bilirubin, ALT, AST, ALP), creatinine
- HBsAg, HBsAb, HBcoreAb; HCV antibody and/or HIV testing can be considered
- Contrast enhanced PET-CT head and neck, thorax, abdomen, pelvis.
- Baseline ejection fraction assessment for patients who are candidates for anthracycline-based therapy and are over the age of 60 and/or have prior history of cardiac disease
- Review of Pathology by UHN hematopathology department.

Frontline systemic therapy

- Among fit patients, R-CHOP chemoimmunotherapy remains the standard approach for patients with Richter's transformation.
- Fit patients (good performance status and minimal/no comorbidities) who have clonally related DLBCL-RT and/or who have had prior therapy for CLL, and achieve a partial or complete response to therapy, should be considered for consolidation allogeneic stem cell transplant with a matched related, haploidentical, or unrelated donor. Donor search testing should be sent upon initiation of induction therapy.
- Less fit or older patients with clonally related DLBCL-RT and/or who have had prior therapy for CLL, who achieve a partial or complete response to therapy, can be considered for autologous stem cell transplant consolidation in exceptional cases. Considerations of appropriateness for autologous stem cell transplant include whether the CLL or DLBCL-RT have TP53 mutation or 17p deletion.
- Patients who have not had prior therapy for CLL in whom there is low suspicion for clonally related RT based on pathology review, can be treated as de novo DLBCL without intensification in CR1. Patients with limited stage transformed disease based on CT or PET-CT scan may be considered for combined modality therapy.
- Given limited clinical trial data guiding the treatment of RT, enrolment to a clinical trial if available is strongly encouraged.

End of treatment investigations:

- History and physical examination; including adverse events and performance status.
- Complete blood count
- Contrast enhanced PET-CT scans of the head and neck, chest, abdomen and pelvis
- Bone marrow biopsy and aspirate if previously involved by RT.

RELAPSED/REFRACTORY DISEASE

Treatment options:

- Enrollment into clinical trials is strongly encouraged
- R-GDP based therapy can be considered in the absence of clinical trials
- As above, fit patients achieving complete or partial response should be considered for consolidation with allogeneic stem cell transplant. Less fit patients can be considered for consolidation for autologous stem cell transplant.
- As above, considerations of appropriateness for autologous stem cell transplant include whether the CLL or DLBCL-RT have TP53 mutation or 17p deletion.
- As above, patients who have not had prior therapy for CLL in whom there is low suspicion for clonally related RT based on pathology review, can be treated as de novo DLBCL, with standard therapies used for such patients (see DLBCL Guidelines)

6.1 Surgery

Surgery does not play a role in the primary management of patients with DLBCL-RT, beyond the need for an adequate excisional biopsy for accurate diagnosis.

6.2 Chemotherapy

The role of chemotherapy in primary management of DLBCL-RT is described above.

6.3 Radiation Therapy

Radiation can be considered in the management of patients similar to de novo DLBCL.

6.4 Oncology Nursing

Refer to general oncology nursing practices

7. Supportive Care

7.1 Patient Education

Refer to general patient education practices

The challenging prognosis of patients with DLBCL-RT should be discussed with patients. Patients should be encouraged to discuss advanced care planning with family, and early palliative care

referral for symptom management should be considered.

7.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Refer to general oncology palliative care guidelines

8. Follow-up Care

Monitoring

- Document physical examination of previously involved areas.
- At each subsequent visit: Document history and physical examination, toxicities, performance status; follow blood counts and other biochemistries
- Patients should be followed indefinitely given the concomitant CLL diagnosis
- Counselling regarding physical and psychological health issues, including impact of treatment on quality of life, management of fatigue, fertility and contraception, cardiovascular fitness, risk of recurrence, and risk of second malignancy. Smoking cessation for smokers.

Oncology Clinic Follow-up Frequency:

First year	-	Visits every 3 months
2 - 3 years	-	Visits every 4 months
4 - 5 years	-	Visits every 6 months
> 5 years	-	annual follow up

9. References

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