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Onco News

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From the Desk of Editor

Dear Readers!

Over whelming response to first two issues of Onco-News encouraged us to make it more comprehensive and informative bulletin.

I am optimistic that short and updated information on various diagnostic, therapeutic and other aspects of oncology will keep all of you well versed of various malignancies.

In this issue, I will be updating Chronic Lymphocytic Leukemia (CLL), which was once considered uniformly a slow progressive disease.

In India, CLL represent only 5-10% of leukemias. CLL has strong familial aggregation.

In last one decade lot of changes has happened in diagnostic, moluculer and therapeutic aspects of this disease. Moving from conventional alkylator based therapy, chemo immunotherapy is now standard of care for relatively younger and fitter patients. Monoclonoal antibodies like Rituximab, Ofatumumab, Obinutuzumab have changed the algorithm of treatment. But the real and exciting development is availability of drugs like Ibrutinib (Bruton's tyrosone kinase inhibitor), Idelalisibe (Posthoinositide 3-Kinase inhibitor) and Venitoclax (Bcl-2 Inhibitor).

You can send your valuable suggestions and comments either through e-mail or twitter.

With regards

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INTRODUCTION :

CHRONIC LYMPHOCYTIC LEUKEMIA

CLL is one of the most common B-cell malignancies. The disease is characterized by the accumulation of small lymphocytes with minimal cytoplasm and clumped nuclear chromatin. Although it is not possible to reliably differentiate between CLL and other forms of B-cell malignancies using microscopy alone, the presence of a raised lymphocyte count in an elderly patient, coupled with the presence of increased numbers of small lymphocytes with this characteristic appearance should raise diagnostic suspicion of CLL.

In CLL, the abnormal B-cells appear morphologically mature but are immunologically incompetent. In addition, the overgrowth of malignant B-cells in CLL can crowd out the other types of blood cells in the bone marrow, hindering the production of red blood cells (erythrocytes), other important leucocytes such as neutrophils and monocytes ; and platelets. As a result, patients with CLL may be anemic, prone to infection and bruise or bleed easily.

Natural History of CLL:

CLL has traditionally been thought of as an indolent disease with a long clinical course. However, in reality, the natural history of the disease varies widely between individuals. Some patients present with an aggressive disease

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that progresses rapidly and has a median survival of less than 3-4 years. These patients commonly die due to complications of the disease. Other patients follow a more indolent course and may live with CLL for 10 years or more, unless they die of another cause. Patients with aggressive biology tend to present with more advanced disease which is relatively resistant to treatment. On the other hand, patients with non-aggressive biology are often diagnosed early in the course of the disease and are often in the older age group.In a minority of patients, the disease may transform to a more aggressive lymphoma. This is known as Richter's transformation.

Diagnosis:

International workshop on CLL used diagnostic criteria:

1. A blood monoclonal B lymphocyte counts >$5x10^9$, with < 55% of the cells being prolymphocyte.
2. B-Lymphocyte monoclonal should be demonstrated with cells expressing B-cell surface antigen (CD19, CD20, CD23) low density surface immunoglobulin (M or D), and CD5.

Staging:

In clinical practice, it is important to establish the stage of a patient's CLL in order to establish a prognosis and make decisions about treatment.

The two most widely used staging systems for CLL are the Rai and Binet systems. They are based principally on physical examination of the patient and on blood counts. Both Rai and Binet define the clinical stage of a patient's CLL based on the presence of anaemia and/or thrombocytopenia, as well as the number of regions with enlarged lymph nodes, and whether or not the patient has a palpably enlarged liver or an enlarged spleen.

The Rai system is the most widely used staging system for CLL

System	Clinical features	Estimated median survival (years)
Rai stage		
Low risk (stage 0)	Lymphocytosis in blood and marrow only	11.5
Intermediate risk (stages I and II)	Lymphadenopathy, splenomegaly +/- hepatomegaly	11.0 (I) 7.8 (II)
High risk (stages III and IV)	Anemia, thrombocytopenia	5.3 (III) 7.0 (IV)

Other prognostic factors:

In addition to clinical stage, a number of other prognostic factors have been investigated in CLL as a way of predicting the natural course of the disease in an individual patient. In recent years, numerous genetic approaches have provided new markers for prognosis and response prediction viz. p53 mutations/del(17p), mutated IgVH, NOTCH1 mutation, SF3B1 mutations etc. among others.

Biology of 17P:

One of the most dreaded abnormalities in CLL is del 17p. This abnormality is found in 3-10% of CLL patients eligible to start treatment and in 30-50% of patients with relapsed/refractory CLL. Its presence is associated with aggressive, treatment-resistant disease.

The deletion results in the loss of a gene called TP53 that is involved in preventing the proliferation of abnormal cells that have mutated DNA. Sometimes also known as the 'guardian of the genome', TP53 senses the presence of abnormal DNA and triggers either DNA repair mechanisms or cell death.

The prevalence of del 17p is much higher in relapsed-refractory CLL than in untreated CLL. This is likely explained by chemotherapy-based treatment selecting for growth of resistant sub-clones such as del(17p).This has important

implications for treatment selection and sequencing, suggesting that there is a clear unmet need for a novel treatment option with efficacy against del 17p that will not favour outgrowth of del 17p sub-clones.

Treatment strategies in CLL (According to NCCN Guidelines):

Standard management for early stable disease is a 'watch and wait' strategy with blood cell counts and clinical examinations performed every 3 months.

Current guidelines on the treatment of CLL recommend that treatment should only be given to patients with active and symptomatic disease.

FRONTLINE TREATMENT (without del17p/TP53 mutation):

For younger, fitter patients treatment of choice is chemoimmunotherapy with FCR (Fludarabine + Cyclophosphamide + Rituximab).Alternative treatments include: FR, BR (Bendamustine + Rituximab) and Ibrutinib

For elderly patients and younger patients with significant comorbidities the treatments of choice are Obinutuzumab + Chlorambucil, Ibrutinib. Alternative treatments include: BR, Chlorambucil.

For frail patients with significant comorbidities the treatments of choice are Ibrutinib, Obinutuzumab+Chlorambucil. Alternative treatments include: Rituximab+Chlorambucil, Rituximab, Obinutuzumab.

RELAPSED/REFRACTORY CLL (without del17p/TP53 mutation):

For younger, fitter patients the treatment of choice is Ibrutinib. Alternative treatments include: FCR, R-CHOP, FC+Ofatumumab etc.

For patients with significant comorbidities the treatment of choice is Ibrutinib. Alternative treatments include BR, Reduced dose FCR, Rituximab+Chlorambucil etc.

PATIENTS WITH del17p/TP53 MUTATIONS :

The treatment of choice for both frontline and relapsed/refractory patients is Ibrutinib.

BTK Inhibitors:

Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor. Ibrutinib was developed to specifically target and selectively inhibit BTK in malignant B-cells. BTK is a key mediator of at least three critical B-cell pro-survival mechanisms that occur in parallel; regulating B-cell apoptosis, cell adhesion and lymphocyte migration and homing. By selectively inhibiting BTK, ibrutinib has demonstrated clinical efficacy in a wide variety of B-cell malignancies including CLL, SLL (Small Lymphocytic Lymphoma), MCL (Mantle Cell Lymphoma), WM (Waldenstrom Macroglobulinemia), FL (Follicular NHL), DLBCL (Diffuse Larg B-cell Lymphoma) and multiple myeloma.

In its registration trial, at 3-year follow-up Ibrutinib showed an Overall Response Rate (ORR) of 79% including a Complete Remission (CR) rate and Partial Remission (PR) rate of 6% and 65% respectively. Median Progression Free Survival (mPFS) was not reached and 30 month and PFS Rate was 76%.

BOOK - POST

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