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HIGH RISK CHRONIC LYMPHOCYTIC LEUKEMIA: PRIORITIZING TREATMENT STRATEGIES.

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ABSTRACT

CLL is a lymphoid malignancy described by the amassing and proliferation of nonfunctional and monoclonal small CD5/CD19/CD-20/CD23-positive lymphocytes in the blood, bone marrow, and lymphoid tissues. It is the most well-known adult leukemia in the India, with 20,000 new cases and approx. 5000 deaths in 2014. CLL is fundamentally a malady of old age with the middle age at finding being 70 years; its frequency in the male populace is accounted to be twice that of the female populace. Finding of CLL requires the vicinity of no less than 5,000 monoclonal mature B-lymphocytes per microliter in the peripheral blood. The treatment methodologies of CLL are exceedingly individualized with patients in the early and stable phases of CLL not requiring treatment. Be that as it may, those with clinically advanced disease will require treatment. Cytotoxic medications, for example, the alkylating agents (chlorambucil, cyclophosphamide, and Bendamustine), have been the pillar of chemotherapeutic treatment in CLL. In any case, their absence of specificity for CLL cells and toxicity to normal cells, especially hematopoietic and immune cells, have restricted their efficacy. Other treatment strategies incorporate purine nucleoside analogs (PNA, for example, Fludarabine and immunotherapeutic agents, for example, anti CD20 monoclonal antibodies (Rituximab, Ofatumumab and Alemtuzumab). A few regimens utilizing the mix of immunotherapy with chemotherapeutics medications are additionally as of now being utilized as a part of the treatment of CLL. A treatment regimen combining Fludarabine, cyclophosphamide, and Rituximab (FCR) is right now the gold standard treatment for CLL and has likewise demonstrated reaction in relapsed/obstinate cases.

KEYWORDS: Rituximab, Ofatumumab, Alemtuzumab, Fludarabine, cyclophosphamide, and Rituximab (FCR).

INTRODUCTION

CLL is the most prevalent leukemia in the India with about 100,000 patients living with the disease.[1-3] Genetics and molecular genetics have subsidized to clarify the biological bases of the clinical heterogeneity of CLL. Recently, our knowledge towards molecular genetics of CLL has significantly widened, offering impending new clinical inferences. Mutations of TP53 and ATM include prognostic data independent of FISH cytogenetic stratification.[4-7] Furthermore, next generation sequencing technology have already identified unknown genomic modifications in CLL.

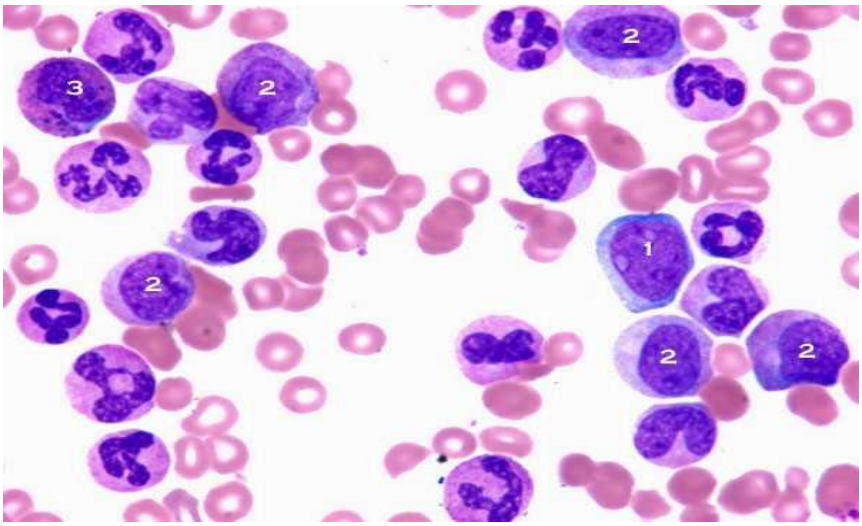

Figure:-1 Histopathology of CLL

Treatment of CLL has progressed immensely in the previous two decades resulted in enhanced survival of patients with this disease. Alkylating agents and glucocorticoids were initially utilized as a part of treatment of CLL in the 1960's. Purine analogs (cladribine, fludarabine and pentastatin) were made available in the 1980's. Development of rituximab by IDEC pharmaceuticals and its consequent FDA approval for treatment of non-Hodgkin lymphoma in 1997 introduced profoundly viable chemo immunotherapy regimens which is still the standard treatment for CLL. FCR (Fludarabine, cyclophosphamide, rituximab) prompts a general reaction rate of ~92% and a complete reaction rate of 65% when infused to untreated patients with CLL.[8-11] Both fludarabine-and pentastatin-based regimens have high recurrence rate (71%) of neutropenia in CLL patients, and also prolonged suppression of T cell-mediated immunity. The lion's share (90%) have a simultaneous medicinal condition,

while 50% convey one or more significant comorbidity (e.g., cerebrovascular disease, coronary artery disease, diabetes mellitus).[12]

Recent clinical trials in CLL (Table1), including clinical study which are evaluating newer chemotherapy agents, (for example, Bendamustine), have tight eligibility criteria for participation in clinical trials. Therefore, on the grounds that[13]

a) Current chemo-immunotherapy regimens generally have severe adverse event in majority of the patients;
b) There is a clonal development and Fludarabine resistant in light of chemotherapy in CLL; and
c) Due to absence of a remedial methodology, and additionally high risk associated with stem cell treatment, there is an intense need in new treatment approaches for CLL.

Table 1:- New therapeutic therapy for CLL

S.No.	Drug	Target	Mechanism
1	Ibrutinib	BTK	Covalent Kinase Inhibitor
	CC-292	BTK	Covalent Kinase Inhibitor (Binds Cys 481)
	ONO-4059	BTK	Covalent Kinase Inhibitor (Binds Cys 481)
2	Idelalisib	PI3Kδ	Competitive Kinase Inhibitor,PI3Kδ
	IPI-145	PI3Kδ	Competitive Kinase Inhibitor,PI3K δ and ϒ
3	ABT-199	BCL-3	Small Molecule BH3 mimetic
4	Obinutuzumab	CD20	Type 2 Antibody

Genetic Alterations in CLL

CLL cells generally carry deletions at 13q14, 11q22–q23, or 17p13 or usually have an additional duplicate of chromosome 12 (trisomy 12); The approach of NGS technology, combined with gene CNV investigations, have distinguished extra genetic mutations in CLL, for example, transformations in NOTCH1, SF3B1, and BIRC3. Such transformations could be utilized as possible therapeutic targets or as biomarkers that can recognize among patients who may have divergent clinical results.[14-17]

NOTCH1 usually translates a ligand-activated translation variable (NOTCH1) that directs a few downstream pathways that prompt the separation of hematopoietic progenitor cell into immature T cells and of matured B cells into antibody secreting cells. Transformations in NOTCH1 happen in ~60% of T-ancestry acute lymphoblastic leukemia.[18-21] In CLL, NOTCH1 mutation have been recognized in ~10% of recently analyzed cases, however in

20% of relapsed CLL cases. NOTCH1 mutation are likewise more frequent in CLL cell population that express unmutated IGHVs having trisomy 12. Cases with NOTCH1 mutation seem to have a particular gene expression profile and characterize a high-risk subgroup of patients with clinical results equivalent to those cases with disruption in TP53, independent of other known risk factor.[22-24] NOTCH1 mutation in CLL are confined to the C-terminal PEST [proline (P), glutamate (E), serine (S), and threonine (T)], which ordinarily restrains the intensity and span of NOTCH1 signaling. One intermittent transformation (c.7544_7545delCT) represents ~77% of all NOTCH1 mutation in CLL and can be quickly identified by a straightforward PCR–based technique, giving a potential approach for a first-level screening of NOTCH1 mutations.[25-26]

SF3B1 translates the splicing factor 3B sub-unit 1 (SF3B1), which is a basic segment of both major (U2-like) and minor (U12-like) spliceosomes that are utilized for the exact extraction of introns from pre-mRNA. Mutations in SF3B1 were seen in ~10% of recently analyzed CLL cases and in ~18% of cases with late stage disease requiring treatment. SF3B1 mutations are obviously acquired amid clonal development, and the sub-clones harboring SF3B1 transformations can increment after some time, autonomously of cytoreductive treatment.[27] Such mutations assume a part in leukemia pathogenesis and progress by the grouping these transformations in hot spots within HEAT domains. Since SF3B1 directs the gene splicing controlling cell-cycle progression and apoptosis, mutation in SF3B1 may enhance CLL cell multiplication and survival.[28]

BIRC3 translates the baculoviral inhibitor of apoptosis (IAP) repeat–containing 3 protein (BIRC3), which belongs to the IAP group of proteins that can repress apoptosis by binding to tumor necrosis factor (TNF) receptor–associated factors 1 and 2 (TRAF1 and TRAF2), perhaps by meddling with activation of ICE-like proteases (caspases).[29-31] BIRC3 usually act as an E3 ubiquitin–protein ligase that controls nuclear element κB (NF-κB) signaling, thus promoting NF-κB signaling while stifling activation of noncanonical NF-κB signaling. Activation of NF-κB signaling can lead to the development and survival of CLL cells in vitro and in vivo. BIRC3 transformations in CLL are anticipated to disrupt the C-terminal RING area, which is vital for proteasomal degradation of MAP3K14 (mitogen-activated protein kinase 14) by BIRC3.CLL cells harboring mutations in BIRC3 show NF-κB activation and seem less receptive to routine chemotherapy than CLL cells without such transformations.[32]

Clinical Importance of ATM Variations in CLL

Deletion of 11q22-q23 was generally related to CLL progression, poor reaction to alkylator and fludarabine-based chemotherapy and, eventually, short survival. The introduction of chemo immunotherapy based treatments has changed the prediction of subjects with this hereditary variation. The prognostic effect of ATM mutations in CLL has been examined in few clinical studies, because of the complex DNA's sequencing method and difficulty in identifying somatic mutations and germline transformations from SNP.[33]

In vitro, CLL cells with transformations influencing either one or both ATM alleles show imperfect apoptosis in light of radiation and chemotherapy-instigated DNA damage. On the other hand, 11q22-q23 deleted CLL with residual ATM allele protect the DNA damage reaction, proposing that loss of a single ATM allele won't not be adequate to activate chemo refractoriness.[34] Therefore, when utilizing chemotherapy alone, ATM transformation could be one mechanism accounting chemo-refractory CLL in which no distortions of TP53 are distinguished.

ATM deletion represent a single biomarker of poor anticipation in CLL patients, especially in the event that they are treated with chemotherapy regimens not containing rituximab. Since the addition of rituximab with chemotherapy (i.e. FCR) prompts an enhanced result in CLL harboring 11q22-q23 deletion. In any case, even in the immune chemotherapy, 11q22-q23 deleted patients have a short PFS and, consequently, may be especially suited for investigational drug combined with immune chemotherapy for dragging out disease remission.[35]

Closing Remarks

The promising results revealed by targeted treatment have reformed the present treatment strategies for CLL. Both pre-clinical and early clinical study results including novel targeted on treatments firmly recommend that the standard treatment worldview in CLL and B-cell malignancies will change in the following couple of years. Specific consideration ought to be paid to the BCR-targeting agents, ibrutinib and idelalisib, which as of now exhibit empowering action both as single agents and in blend with routine chemotherapy over a mixed bag of B-cell neoplastic conditions, including those with unfavorable hereditary features. In fact, a workup at analysis for TP53 and ATM deletion, and NOTCH1, SF3B1 and BIRC3 transformation empowers a more refined prognostic stratification of subjects. None of these biomarkers, are able to detect early indicator for proper treatment, yet prompts a closer

clinical follow-up. Despite the fact that there are presently no treatment procedures for TP53 disturbed CLL in the elderly, the utilization of low doses of Alemtuzumab has demonstrated feasible. The clinical heterogeneity of CLL subjects seems to mirror the differing molecular variations that drive progression and pathogenesis of CLL. Novel treatments keep on developing in the preclinical stage and will extend the armamentarium of drug combinations in hematologic oncology in the coming decades.

CONFLICTS OF INTEREST STATEMENT

The Authors declare no conflicts of interest.

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