Geographic Diversity and Management of CLL in Indian Patients

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St James’s University Hospital, Leeds, United Kingdom
No conflict of interest to disclose
Overview....

- Epidemiology of CLL in India
- Health system of India
- Real life data on CLL
- Opinion of clinicians treating CLL
- Cultural aspects of treatment
Estimated age-standardized incidence rates (World) in 2018, leukaemia, both sexes, all ages

India
Age-standardized rate (World) 3.2

<table>
<thead>
<tr>
<th>Number of incident cases</th>
<th>42,055</th>
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<tbody>
<tr>
<td>Crude rate</td>
<td>3.1</td>
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<tr>
<td>ASR (World) per 100,000</td>
<td>3.2</td>
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</table>

Cancer Today - IARC, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France - Tel: +33 (0)4 72 73 84 85 - powered by GLOBOCAN 2018
### Epidemiological studies from India.....

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal volume</th>
<th>Authors</th>
<th>Incidence of CLL</th>
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<tbody>
<tr>
<td>Leukaemia at Lucknow- a study of 200 cases</td>
<td>Ind J Cancer 1978;15:28-34</td>
<td>Kushwaha MRS, Bagchi M, Mehrotra RML.</td>
<td></td>
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<tr>
<td>Epidemiological observations on leukaemia in Kerala (A study of 1016 cases over three years),</td>
<td>Ind J Haematol, 1984;2:15-17.</td>
<td>Varghese PR, Elayidom NB, Joseph CD et al</td>
<td>ALL 24%, AML 29.3%, CML 36.7%, CLL 8%, others 2%</td>
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<tr>
<td>Incidence of acute and chronic leukaemia in rural area at tertiary care teaching hospital; a five years of study</td>
<td>Indian Journal of Pathology and Oncology, Oct-Dec 2016;3(4);710-713</td>
<td>Baviskar J B.</td>
<td>AML 23.07%, ALL 26.28%, CML 33.97%, CLL 15.38%, others 1.28%</td>
</tr>
</tbody>
</table>
Studies from major centres...

Chronic Lymphocytic Leukemia in India- A clinico-hematological profile
Agrawal N, Naithani R, Mahapatra M et al

Hematology, June 2007; 12(3): 229-233

- All India Institute of Medical Sciences (AIIMS) 2006-11 year Retrospective study
- Managed around 4000 new patient and 17,500 follow up in haematology OPD per annum during that period
- 95 patients – median age 61 years
- Eighteen (60%) young patients and 35 (54%) older patients required treatment with chlorambucil. (Age cut off 55 years)
- Median survival of study group was 4 years (8 months-13 years).
Review article on epidemiology of NHL in India


<table>
<thead>
<tr>
<th>Subtype</th>
<th>India</th>
<th>Arora et al. [14]</th>
<th>Naresh et al. [13]</th>
<th>Sahni and Desai [31]</th>
<th>China</th>
<th>USA</th>
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<td>6.9</td>
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<td>4.79</td>
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<td>46.85</td>
<td>33.8</td>
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<td>36.4</td>
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<td>FL</td>
<td>10.51</td>
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<td>2.10</td>
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<td>BL</td>
<td>3.38</td>
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<td>1.91</td>
<td>1.42</td>
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<tr>
<td>MALT</td>
<td>2.47</td>
<td>6.1</td>
<td>2.7</td>
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<td>6.31</td>
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<td>15.24</td>
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<td>0.12</td>
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<tr>
<td>PMBCL</td>
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<td>0.2</td>
<td>0.1</td>
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<td>–</td>
<td>0.37</td>
<td>0.4</td>
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<td>0.65</td>
<td>1.9</td>
<td>0.2</td>
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<td>0.09</td>
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<td>1.25</td>
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<td>PTCLN, NOS</td>
<td>5.91</td>
<td>1.9</td>
<td>4.6</td>
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<td>3.27</td>
<td>4.87</td>
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<td>1.11</td>
<td>2.40</td>
<td>2.2</td>
<td>3.67</td>
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<td>1.39</td>
<td>1.0</td>
<td>0.4</td>
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<td>0.23</td>
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<td>1.81</td>
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<tr>
<td>SPTCL</td>
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<td>0.1</td>
<td>–</td>
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<td>0.97</td>
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<td>0.49</td>
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<td>PCCD30+LPD</td>
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<td>MF/SS</td>
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<td>HSL</td>
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<td>0.39</td>
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<tr>
<td>Others</td>
<td>–</td>
<td>9.34</td>
<td>1.87</td>
<td></td>
<td>3.0</td>
<td>1.04</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Total, n</td>
<td>4,026</td>
<td>2,773</td>
<td>935</td>
<td></td>
<td>5,549</td>
<td>77,490</td>
<td>4,337</td>
<td>2,260</td>
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<tr>
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<td>England</td>
<td>Globocan</td>
<td>CIV</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>White</td>
<td>18 381</td>
<td>7·8</td>
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<tr>
<td></td>
<td>Indian</td>
<td>214</td>
<td>5·3</td>
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<table>
<thead>
<tr>
<th>Cancer</th>
<th>Ethnicity</th>
<th>Male</th>
<th>Female</th>
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<td></td>
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<tr>
<td>Leukaemia</td>
<td>White</td>
<td>13 324</td>
<td>4·9</td>
</tr>
<tr>
<td></td>
<td>Indian</td>
<td>163</td>
<td>3·9</td>
</tr>
</tbody>
</table>

Test of heterogeneity by tumour type: South Asian: $\chi^2 = 20·1; P < 0·001$; Black: $\chi^2 = 338·8; P < 0·001$; Chinese: $\chi^2 = 7·1; P = 0·07$
Comparison of MBL between Ugandan and the UK population

Study designed to find the prevalence of Monoclonal B-cell lymphocytosis (MBL) in healthy rural Ugandan population and comparing it with age-and-sex-matched populations from the UK.

This allowed comparison of prevalence across different populations independently of health-care provision.

The prevalence of MBL is broadly similar in rural Uganda and the UK, but substantial qualitative differences exist, with a lower prevalence of CLL-phenotype MBL and higher prevalence of CD5-negative MBL in the Ugandan cohort than in the UK cohort.

Lancet Haematology. 2017 Jul; 4(7): e334–e340. Monoclonal B-cell lymphocytosis in a hospital-based UK population and a rural Ugandan population: a cross-sectional study  Andy C Rawstron, Prof, PhD,*
Does this mean incidence is really low in Indian population?

- In India patients usually present to clinicians only if symptomatic
- Identifying asymptomatic patients from blood test for other reasons is very limited
- Average life span of an Indian is below the median age for CLL
India - A Land of Diversity

- 1.34 billion (Census, March 2017)
- 29 states and 7 Union territories
- 17 major languages and 900 dialects
- Birthplace of 4 major religions of world
- Some of the most beautiful monuments to the dirtiest slums
- Diversity in culture, race, language, religion, economic status etc
- >72% live in village
Health-care System in India

- **GOVERNMENT ROLE**: Central-Financing, legislation, and regulation
  - State- financing, regulation, and direct provision of services

- **PUBLIC SYSTEM FINANCING**: General tax revenue

- **PRIVATE INSURANCE ROLE**: <4% of total expenditure

- **PRIMARY CARE**: Mainly public; some private, especially in urban areas

- **HOSPITALS**: Private nonprofit and for-profit (~63% of beds) and public

- **TOTAL HEALTH EXPENDITURE**: (2013–2014) 4.02% of GDP. Government expenditures 1.5% (lower than the average for low-income countries.)

- **70% of total health expenditure is out-of-pocket payment**

- **Despite various government health schemes, <20% is covered by any form of health coverage.**

- **Health Care Spending per Capita, 2014 is $215**

- **Number of Practising Physicians per 1,000 Population, 2014- 0.7**

- **More than 63 million Indians are faced with impoverishment every year because of catastrophic health care costs.**

### Public
- Universal health-care system
- “Right to health” for all.
- National Health Policy-large rural and poor population
- Rural: Three-tier system: a sub-centre, a primary health centre, and a community health centre.
- Urban areas: Two-tier system with urban health centre followed by general hospital

### Corporate
- Only a fraction of patients can afford
- Mainly urban
- Health insurance: 10% of the population

### Indigenous or traditional systems
- Ayurveda, Siddha, Homeopathy and Unani

### Mission Hospitals
- “No profit no loss basis”
- Fragmented service

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- Ayurveda, Siddha, Homeopathy and Unani
Disease Burden— Disability-Adjusted Life Years (DALY)

Heatmap (causes)- Annual % change 1990 to 2017
DALYs/100,000

- Growing burden of non-communicable diseases including cancer
- Reducing burden of communicable diseases
## Biology of CLL in Indian Patients......

<table>
<thead>
<tr>
<th></th>
<th>Indian study</th>
<th>Western study</th>
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<tr>
<td>17p-</td>
<td>13.3%</td>
<td>7%&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>11q-</td>
<td>13.3%</td>
<td>18%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ZAP70</td>
<td>37%</td>
<td>47%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CD38</td>
<td>44%</td>
<td>29%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ZAP70+C38</td>
<td>26%</td>
<td>23%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unmutated IGVH</td>
<td>36%</td>
<td>40%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>VH1-69; VH3-73; VH3-48; VH2-70; VH3-23; and VH1-03.</td>
<td>10%, 7%, 6%, 5%, 4%, 3%&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>18%</td>
<td>10%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>β2-microglobulin level</td>
<td>36%</td>
<td>33%&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- Limited number of articles
- 2016 ASH Abstract from All India Institute of Medical Science
- 100 patients evaluated


<sup>b</sup>Combined analysis of ZAP-70 and CD38 expression as a predictor of disease progression in B-cell chronic lymphocytic leukemia. Leukemia (2005) 19, 750–758

<sup>c</sup>Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6):1848–54.


<sup>e</sup>The Chronic lymphocytic leukemia patients with a V1-69 gene rearrangement do not have inferior survival with respect to patients that express other unmutated VH genes,” Leukemia Research, vol. 31, no. 2, pp. 245–248, 2007.

<sup>f</sup>Predictive value of β2-microglobulin (β2-m) levels in chronic lymphocytic leukemia since Binet A stages. Haematologica. 2009 Jun; 94(6): 887–888.
NON HODGKIN LYMPHOMA - Low Grade (CLL/SLL, FL, MZL)

1. **Stage 1 & 2**
   Asymptomatic patients can be observed or treated with local RT
   Combined modality chemo-immunotherapy x 3 cycles → local RT

2. **Stage 3 & 4 - Asymptomatic**
   Observation alone or Single agent Rituximab weekly x 4 followed by Maintenance 2 to 3 monthly for 2 years.

3. **Stage 3 & 4 - Symptomatic**
   Chemo-immunotherapy x 6 cycles followed by Maintenance Rituximab for 2 years

*Note:* Symptomatic disease is largely based on the BNLI Criteria which include the following: Subjective symptoms, threatened end organ dysfunction, Bulky disease, Cytopenias, disease progressing steadily (doubling time short).

Choice of regimen should be based on patient age (≤ 65 yr or ≥65 yrs), co-morbidities. It should be dictated by the local expertise. Common regimens include,

- CVP +/- R
- CHOP +/- R
- Bendamustine +/- R
- In CLL, also consider FCR, Ofatumumab-Chl, Alemtuzumab-Rituximab (high risk CLL).
Management of CLL, Indian Guidelines....

Management of Lymphomas: Consensus Document 2018 by an Indian Expert Group

Newer Therapy Options

Indolent B-Cell Lymphoma

Chronic Lymphatic Leukemia/Small Lymphocytic Leukemia

Consider participation in clinical trial with new agents.

1. Ibrutinib
2. Venetoclax (post-ibrutinib)
3. Idelalisib
4. Obinutuzumab or ofatumumab (especially in rituximab refractory)
5. Chemo-immunotherapy
   1. Rituximab (or obinutuzumab in rituximab refractory)
   2. Chemotherapy: fludarabine-cyclophosphamide v/s. CHOP v/s. ibrutinib-bendamustine, etc.
6. Non-chemo combination therapies
   1. Ibrutinib + Venetoclax
   2. Rituximab + Ibrutinib
   3. Rituximab + Venetoclax
7. Post-induction maintenance therapy must be considered in patients who have partial or complete response.
8. p53 mutated (or 17p deleted) disease is generally resistant to conventional therapies. In this subset of patients, allogeneic bone marrow transplant (BMT) must be considered in the young (especially those with a complex karyotype).
Real-life data from a hospital in Delhi. 1250 bedded hospital
Private, for-profit hospital
Pay-out-of-pocket and private insurance

• Retrospective case record audit
• Retrieved records from hospital electronic record with diagnosis of CLL
• Records from May 2009 to May 2019
• N=124

Acknowledgement to Dr. Nitin Sood for providing the data

<table>
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<td>Median Age (Range)</td>
<td>69 (40-91)</td>
</tr>
<tr>
<td>Female:Male</td>
<td>29:95</td>
</tr>
<tr>
<td>Cytogenetics done</td>
<td>40 (32%)</td>
</tr>
<tr>
<td>del17p positive (prior to 1st line)</td>
<td>4/28 (14.2%)</td>
</tr>
<tr>
<td>Other cytogenetic abnormalities</td>
<td>13/28 (46.4%)</td>
</tr>
<tr>
<td>del17p positive (previously treated patients)</td>
<td>2/12 (16.7%)</td>
</tr>
<tr>
<td>Other cytogenetic (previously treated patients) abnormalities</td>
<td>1/12 (8.3%)</td>
</tr>
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### Indication for treatment

<table>
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<th>N(%)</th>
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<tbody>
<tr>
<td>Patients requiring treatment</td>
<td>87 (70%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>35 (40%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>B Symptoms</td>
<td>27 (31%)</td>
</tr>
<tr>
<td>Progressive lymph nodes</td>
<td>23 (26%)</td>
</tr>
<tr>
<td>Progressive lymphocytosis</td>
<td>41 (47%)</td>
</tr>
<tr>
<td>Symptomatic spleen</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>others</td>
<td>5 (6%)</td>
</tr>
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</table>

### Number of Lines of Treatment

- **1st Line**: 70.16129032
- **2nd Line**: 25.80645161
- **3rd Line**: 11.29032258
- **4th Line or more**: 6.451612903

7 patients had major infection requiring hospital admission.
Chemotherapy given

<60, n=24

>60, n=63
2nd line treatment, n=32

Overall Survival

Median follow up 23 months
Survey on Management of CLL from Clinicians

Google survey form was used. 23 questions 10-15mts survey Send to 188 clinicians. 25 responded!!
Demographics

- Do you think CLL is common in India as seen in western population (25 responses):
  - Yes: 80%
  - No: 20%

- What percentage of all Leukaemia is CLL in India (your perception):
  - Median 10 (2-25)

- Median values for various demographics:
  - % requiring treatment: Median 50 (10-90)
  - % of relapsed patients <65: Median 25 (0-90)
  - % of new patients <65: Median 30 (0-70)
  - Relapsed patients seen annually: Median 5 (0-25)
  - New CLL patients seen annually: Median 10 (3-155)
  - % of total patient is CLL: Median 5 (0.5-20)
Investigations done...

- Viral serology
- CXR
- Direct Coombs test
- Serum Immunoglobulin
- Serum Chemistry
- Bone Marrow IHC
- Bone Marrow aspirate and...
- Flow cytometry

Graph showing the frequency of each investigation:
- Always
- Sometimes
- Never
- Not answered

- FISH for del13q
- FISH for del11q
- FISH for del17p
- FISH for add12
- Conventional karyotyping
- TP53 mutation
- IGHV mutational status
- Serum β2-microglobulin
- CT scan of chest, abdomen, and pelvis
- PET scans
- Abdominal ultrasound
- CT scan of chest, abdomen, and pelvis
Guidelines followed and Clinical trials...

ELN- European leukaemia network
IWCLL- International working committee for CLL
BSH- British society of haematology
NCCN- National Comprehensive Cancer Network

Count of Do you conduct any clinical trials in CLL

- Will consider in future: 28.0%
- No: 72.0%
Treatments used......
Reason for not using FCR.....

If FCR is not preferred as first choice the reason for not choosing

- Personal preference: 6 (26.1%)
- Toxicity concern: 21 (91.3%)
- More efficient treatment available: 2 (8.7%)
- Cost concern: 7 (30.4%)
- Local guideline: 0 (0%)
- BR better tolerated: 1 (4.3%)

If toxicity is the concern what type of toxicity

- Neutropenic fever: 22 (95.7%)
- Viral infection: 9 (39.1%)
- Fungal infection: 9 (39.1%)
- Tuberculosis: 3 (13%)
- CMV: 1 (4.3%)
- Myelosuppression: 1 (4.3%)
Allogeneic Transplant

- Yes: 32%
- No: 68%

<table>
<thead>
<tr>
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<tr>
<td>If no reason for not using</td>
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<tr>
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<td>Cost of treatment</td>
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<tr>
<td>Ibrutinib</td>
<td>72%</td>
<td>28%</td>
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<tr>
<td></td>
<td>16%</td>
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<tr>
<td>Venetoclax</td>
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<td>62%</td>
<td>38%</td>
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<tr>
<td>Other newer agents</td>
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</table>
Response assessment

25 responses

- Clinical: 23 (92%)
- Haematological: 24 (96%)
- Bone Marrow: 9 (36%)
- CT scan: 9 (36%)
- PET scan: 3 (12%)
- Minimal Residual Disease (MRD): 6 (24%)
Treatment funding source.....
Comments....

• It is unfortunate that we can only juggle between BR, R-COP and Chlorambucil.
• We sometimes use oral metronomic chemotherapy, combination of oral etoposide, cyclophosphamide and prednisolone.
• The cost of Ibrutinib and venetoclax are extremely prohibitive. It is truly frustrating to treat CLL in this regard.
• We have the means to do MRD at the end of first-line treatment but do not see any purpose to wasting money on it.
• FCR is extremely toxic and costly. With the limited hospital bed availability it would be difficult to sustain such length hospital admissions. Moreover, our patients are biologically older and more frail. Sometimes, BR and R-COP tolerance is also a major concern.
• Many of the drugs are costly to be used in India. Medical insurance and govt help is not usual
• I believe it is underdiagnosed as well as under reported.
Cultural aspects.....
Conclusions

- More epidemiological studies are needed before concluding that CLL has low incidence in Indian population.
- Over the next few years establishment of real world data registry for CLL in India. Advise and support from established registries will be very helpful.
- Geographical difference in the incidence and biology will help us to understand the pathophysiology of disease better. Collaborative research like Ugandan MBL study in Indian population.
- Treatment of CLL has to go a long way to catch up with rest of the world.
- Cost of the new drugs are much beyond the scope of majority of Indian patients.
- We need to think about different costing model for countries like India.
- India needs to have its own trial portfolio to guide the treatment of CLL for regional population.
- Collaborative research with established groups in IWCLL will be very helpful.
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