Therapy of Elderly Diffuse Large B Cell Lymphoma: Can we optimise outcome in 2012?

Dr Paul Fields
Guys and St Thomas’, Kings College Hospitals, London
SIOG 27th October 2012

Scale of the problem

DLBCL
- Most frequent type of B cell NHL rising incidence with age
- 2/100000 20-24 Years
- 45/10000 65-64 Years
- 112/100000 80-84 Years (Yancik et al 2004)
- Few elderly patients entered into clinical trials

General population
- Predicted by 2007-2015 number of people in EU over 65 years to rise by 22% and number over 80 by 50% (Mora and Zucca 2007)

Specific issues: DLBCL and the Elderly

1) Physiological – reduced critical organ function
2) Pathological – presence of allied co-morbid conditions
3) Disease biology – is elderly DLBCL the same disease as in younger population?
4) Assessment of the elderly DLBCL patient – is it optimal?
5) Optimisation of the current Gold standard – can we treat more patients with curative intent?

Fall off in functional physiological reserve

Renal: GFR falls by 1ml/minute per year over age 40
- Clearance affected: platinums, etoposide and methotrexate

Hepatic: Liver mass decreases with age, decreased portal blood flow albumin production and p450 – modifying PK properties of Doxorubicin and vincristine

Haematological: Decreased marrow cellularity, decreased sensitivity of ageing stem cells to Erythropoietin, increased haematological toxicity with myelotoxic agents

Immunological: Immunosenescence: Age related decreased T cell responses, thymic atrophy, accumulation of anergic memory T cells, deficiencies in cytokine production.

Co-Morbidities and DLBCL

Co-morbidity was defined as life shortening illnesses that were present at the time of lymphoma diagnosis:

In a study of 7600 Cancer patients: 2.9 CM conditions present in years 55-64 compared to 4.2 greater that 75 years (Pal & Huma JCO 2010)

Specific to aggressive NHL: Eindhoven Cancer Registry (Janssen-Hoopen 2005):

79% over 60 have a Co-Morbidity illness at presentation compared to 48% less 60 years. Of these 40-50% were high impact. The chance of dying with high impact Co-Morbidity was doubled compared to no having no co morbidity.

Multivariate analysis: Lower OS was independently associated with higher IPI and concomitant CM.
3) Disease biology of DLBCL in the Elderly

Complete remission falls with age:
- More chemo resistant tumours
- Increase with ABC subtype with increased age
- More favourable translocations more prevalent in younger age groups i.e. IGH/IRF4 fusions (Saleverna et al. Blood July 2011)
- Increased EBV/DLBCL - associated with a poorer prognosis (24 months median OS) : New WHO 2008 entity described in the elderly

Proportion of activated B cell like subtype among de novo DLBCL Increases with Age (French series)

Pathophysiology of EBV DLBCL

Can we do better with elderly DLBCL?
- Can we treat more patients with DLBCL with curative intent
- How can we improve assessment of these patients
- What are the important qualitative predictors of outcome in this group and can they be optimised / incorporated to improve outcome
- What future areas of research are needed?
What are the categories?

1) Fully fit suitable for curative treatment
2) Fit, but vital co-morbid contraindications i.e. Cardiac
3) Frail, not fit for any curative treatment

R-CHOP studies

- Proof of principle in elderly
- But caveats of exclusion criteria
- Not wholly representative of typical elderly population – certain Co-Morbidities excluded particularly cardiac often excluded from Gold standard therapy i.e. R-CHOP
- Can we offer appropriate curative intent to these patients?

R-CHOP substitutes

R-CHOP
Can we treat R/CHOP contra indicated patients with curative intent
R-C/HOP – discussion at NCRN HGNHL subgroup 2006

Replace doxorubicin with:
1) Etoposide – Canadian BCC group
2) Gemcitabine – tested R-GCVP – UK approach

Risk of Doxorubicin induced chronic Heart failure
Increase with advanced age

Increasing risk with cumulative dose

Trial regimen / outline

R-GCVP

- Patient unsuitable for R-CHOP
- Initial R-GCVP
- Reassess After 2 Cycles
- End of Treatment

At median follow up of 22.8 months

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>Not reached</td>
</tr>
<tr>
<td>OS rate at 1 year</td>
<td>63.8% (95% CI: 55.6-74.9)</td>
</tr>
<tr>
<td>OS rate at 2 year</td>
<td>55.1% (95% CI: 42.3-67.9)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>16.6 months</td>
</tr>
<tr>
<td>PFS rate at 1 year</td>
<td>53.3% (95% CI: 40.3-65.7)</td>
</tr>
<tr>
<td>PFS rate at 2 years</td>
<td>49.3% (95% CI: 36.7-62.0)</td>
</tr>
</tbody>
</table>
**Aspiration for management DLBCL in 2012**

**Diagnosis of elderly DLBCL**

- Co-morbidity assessment
- Functional assessment
- Abbreviated CGA
- Patient discussion

**Categorisation**

- Fit for curative treatment
- Intermediate
- Not fit for curative treatment

- R-CHOP
- R-CHOP if Cardiac
- Contraindications

**Optimisation**

- Pre Phase therapy
- Palliative control

**Abbreviated CGA**

- Categorization

**Conclusions**

- Increasing knowledge of (different) biology elderly lymphoma and design of rational targets appropriate to biology i.e. Specific targeting ABC (Revimid, Velcade)
- Development of novel agents with similar clinical efficacy but equivalent/to less toxicities. (Proposed new NCRN Phase II trial :
  - R-GCVP vs. CMC544–R-CVP, Cl Dr A McMillan)
- Development of "user friendly" abbreviated CGA assessments tailored to individual patients – some groups addressing this i.e. GB/ VES13 : And then to complete studies to test the intervention.
- Will increase elderly recruitment to clinical trials