IL SISTEMA GRADE NELLA PRODUZIONE DI LINEA GUIDA

ATTO BILLIO
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## Before GRADE

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Source of evidence</th>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>SR, RCTs</td>
<td>A</td>
</tr>
<tr>
<td>II</td>
<td>Cohort studies</td>
<td>B</td>
</tr>
<tr>
<td>III</td>
<td>Case-control studies</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Case series</td>
<td>C</td>
</tr>
<tr>
<td>V</td>
<td>Expert opinion</td>
<td>D</td>
</tr>
</tbody>
</table>

SR = Systematic Reviews, RCTs = Randomised Controlled Trials
GRADE
Grades of Recommendation Assessment, Development and Evaluation

- Aim: to develop a system for grading
  1. the quality of evidence
  2. the strength of recommendations
WHAT IS THE BEST FIRST LINE THERAPY IN ADVANCED CLL IN NEED OF THERAPY?
P atient
I ntervention
C omparison
O utcome
IS THE COMBINATION OF RITUXIMAB AND BENDAMUSTINE NON INFERIOR THAN RITUXIMAB + FC IN PROLONGING PFS IN FIRST LINE ADVANCED CLL IN NEED OF TREATMENT?
PICO MODEL

- **POPULATION**: UNTREATED CLL IN NEED OF THERAPY
- **INTERVENTION**: R+BENDAMUSTINE
- **COMPARISON**: R-FC
- **OUTCOMES**: PFS
Quality of evidence across studies centered on OUTCOMES

Outcome #1
Outcome #2
Outcome #3

Quality:
Quality:
Quality:
Very low
Low
Moderate
Critical
Outcome
Outcome
Outcome
Outcome
Critical
Important
Important
Not important
Select outcomes
Rate importance
Quality rating outcomes across studies
Grade down or up
Overall quality of evidence
High
Moderate
Low
Very low
Determinants of quality

What lowers quality of evidence? 5 factors:

- Methodological limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision of results
- Publication bias
Assessment of detailed design and execution (risk of bias)

For RCTs:
- Lack of allocation concealment
- No true intention to treat principle
- Inadequate blinding
- Loss to follow-up
- Early stopping for benefit
### Look for explanation for inconsistency
- patients, intervention, comparator, outcome, methods

### Judgment
- variation in size of effect
- overlap in confidence intervals
- statistical significance of heterogeneity
- $I^2$
Indirect comparisons
- Interested in head-to-head comparison
- Drug A versus drug B
- Tenofovir versus entecavir in hepatitis B treatment

Differences in
- patients (early cirrhosis vs end-stage cirrhosis)
- interventions (CRC screening: flex. sig. vs colonoscopy)
- comparator (e.g., differences in dose)
- outcomes (non-steroidal safety: ulcer on endoscopy vs symptomatic ulcer complications)
Small sample size

- small number of events
- wide confidence intervals
- uncertainty about magnitude of effect
- Reporting of studies
  - publication bias
    - number of small studies
# GRADE evidence profile

**Author(s):** YFY, HJS, EAA  
**Date:** 2008-09-14  
**Question:** Should Parenteral anticoagulation be used for patient with cancer?  
**Settings:** Outpatient  

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Mortality at 12 months (follow-up 1-7 years)</th>
<th>Major bleeding (follow-up 1-7 years)</th>
<th>Minor bleeding (follow-up 1-7 years)</th>
<th>DVT (follow-up 1-7 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of studies</strong></td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>randomized trial</td>
<td>randomized trial</td>
<td>randomized trial</td>
<td>randomized trial</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>no serious limitations</td>
<td>no serious limitations</td>
<td>no serious limitations</td>
<td>no serious limitations</td>
</tr>
<tr>
<td><strong>Inconsistency</strong></td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td><strong>Indirectness</strong></td>
<td>no serious indirectness</td>
<td>no serious indirectness</td>
<td>no serious indirectness</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td><strong>Imprecision</strong></td>
<td>no serious imprecision</td>
<td>serious¹</td>
<td>serious¹</td>
<td>very serious²</td>
</tr>
<tr>
<td><strong>Other considerations</strong></td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>reporting bias³</td>
</tr>
<tr>
<td><strong>Parenteral anticoagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relative (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Absolute</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Importance</strong></td>
<td>CRITICAL</td>
<td>CRITICAL</td>
<td>CRITICAL</td>
<td>IMPORTANT</td>
</tr>
</tbody>
</table>

1 The 95% confidence interval includes both no increased risk of bleeding as well as substantial increased risk of bleeding  
2 Only 2 events in the placebo group  
3 Only 2 trials reported DVT - reporting bias may be present
Formulate recommendations:

Clinical question
Select outcomes
Rate importance
Quality rating outcomes across studies

Grade down or up

High
Moderate
Low
Very low

Overall quality of evidence

Outcome: Critical
Outcome: Critical
Outcome: Important
Outcome: Important
Outcome: Not important
GRADE: Factors influencing decisions and recommendations

- Quality of Evidence
- Balance of desirable and undesirable consequences
- Values and preferences
- Cost
Categories of recommendations

- **STRONG**: the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

- **WEAK**: the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident.

Recommend

Suggest
## Ideal GRADE approach

<table>
<thead>
<tr>
<th>Elements</th>
<th>Advantage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review</td>
<td>Follows international standards</td>
<td>Access to methodologist</td>
</tr>
<tr>
<td>GRADE Tables</td>
<td>Methodologically rigorous</td>
<td>Initially more resource intensive, long-term savings</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Easily maintainable</td>
<td></td>
</tr>
<tr>
<td>Strength of recommendations</td>
<td>Fully transparent process</td>
<td></td>
</tr>
</tbody>
</table>
Formulate recommendations:
• For or against (direction)
• Strong or weak (strength)

By considering:
- Quality of evidence
- Balance benefits/harms
- Values and preferences

Revise if necessary by considering:
- Resource use (cost)

Rate overall quality of evidence across outcomes based on lowest quality of critical outcomes:
• “We recommend using…”
• “We suggest using…”
• “We recommend against using…”
• “We suggest against using…”