NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™

Chronic Myelogenous Leukemia and Multiple Myeloma

Overall management of Chronic Myelogenous Leukemia and Multiple Myeloma from diagnosis through recurrence is described in the full NCCN Guidelines® for Chronic Myelogenous Leukemia and the NCCN Guidelines for Multiple Myeloma. Visit NCCN.org to view the complete library of NCCN Guidelines.
About the NCCN Evidence Blocks™

NCCN Evidence Blocks™ are intended as a visual representation of five key measures that provide important information about specific recommendations contained within the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The goal is to provide the health care provider and the patient information to make informed choices when selecting systemic therapies based upon treatment, supporting data, and cost. These measures may be used to understand the clinical and scientific rationale for specific recommendations and estimates of the economic impact of the recommendations. These measures may also be used to educate providers and patients, and to be a starting point for shared decision-making considering the patient’s own value system.

With the wide range of evidence-based potentially appropriate therapies, clinicians and patients must choose the one treatment that is most appropriate for the individual taking into account what matters most to the patient. For more than 20 years, the National Comprehensive Cancer Network® (NCCN®) has developed and published the NCCN Guidelines® based on critical analysis of the evidence by multidisciplinary expert clinicians and reaching consensus on which interventions constitute appropriate care.

As sub-specialists, panel members have the capacity to track and incorporate disease-specific data that has developed over the past several decades. In a rapidly evolving field like oncology, thousands of new publications are released each year adding to the existing body of knowledge and resulting in improvement in outcomes. Experts are able to integrate new findings with existing information to determine what the evolving standard of care should be for a given disease state. Implicit in the evaluation of each treatment is the efficacy and expected associated toxicities, as well as the quality, quantity, and consistency of the evidence supporting the recommendation. The NCCN Evidence Blocks™ will make the panels’ assessments of these parameters more transparent to the users of the NCCN Guidelines.

NCCN Evidence Blocks™ Development

To develop the NCCN Evidence Blocks™, NCCN Panel members score each measure using a standardized scale from “1” to “5” with “1” being the least favorable and “5” the most favorable. For efficacy and safety, panel members use both their knowledge of the published data—often developed in highly selected patients—and their clinical experience with the treatments in the real-world patient population. Quality and consistency of the data are rated using the panel members’ knowledge of the data supporting the treatment. Affordability is rated using the panel members’ knowledge of the overall cost of the regimen.

Resulting data are analyzed and final scores based on all responding panel members, rounding to the closest whole number. These scores are then used to build the 5 x 5 table that constitutes the NCCN Evidence Block™ for the intervention. Each column in the Evidence Block corresponds to an outcome characteristic. From left to right the outcome characteristics are efficacy (E), safety (S), quality and quantity of evidence (Q), consistency of evidence (C) and affordability (A). The rows of the block are shaded in from bottom to top representing the corresponding score for each measure.

Using the NCCN Evidence Blocks™

The use of a graphical representation of the measures through NCCN Evidence Blocks™ allows for the efficient scanning and interpretation of multiple therapy options in a very efficient manner. When the NCCN Evidence Blocks™ are placed on the NCCN Guidelines algorithm, a user can quickly scan a group of potentially appropriate interventions and make treatment recommendations based on what is most important to the patient. Some patients will want an emerging therapy even with limited data; others will be most concerned about the expected side effects of the treatment indicated in the safety column. Still others may be very sensitive to cost. By considering the attributes of the range of possible therapies, the health care provider and the patient can discuss the benefits and drawbacks of each option and come to a decision most acceptable to the individual.
NCCN Evidence Blocks™ Categories

Panel members used the following criteria to score the measures.

**[E]** The Efficacy measure is the extent to which an intervention is helpful in prolonging life, arresting disease progression, or reducing symptoms of a medical condition. The scale used to measure efficacy is:

- **5 (Highly effective):** Often provides long-term survival advantage or has curative potential
- **4 (Very effective):** Sometimes provides long-term survival advantage or has curative potential
- **3 (Moderately effective):** Modest, no, or unknown impact on survival but often provides control of disease
- **2 (Minimally effective):** Modest, no, or unknown impact on survival and sometimes provides control of disease
- **1 (Palliative only):** Provides symptomatic benefit only

**[S]** Safety refers to the assessment of the relative likelihood of side effects from an intervention with fewer side effects being scored highly. The scale used to measure safety is:

- **5 (Usually no meaningful toxicity):** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
- **4 (Occasionally toxic):** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
- **3 (Mildly toxic):** Mild toxicity that interferes with ADLs is common
- **2 (Moderately toxic):** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
- **1 (Highly toxic):** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Note: For significant chronic or long-term toxicities, score decreased by 1

**[Q]** Quality and quantity of evidence refers to the number and types of clinical trials relevant to a particular intervention. To determine a score, panel members may weigh the depth of the evidence, i.e., the numbers of trials that address this issue and their design. The scale used to measure quality of evidence is:

- **5 (High quality):** Multiple well-designed randomized trials and/or meta-analyses
- **4 (Good quality):** Several well-designed randomized trials
- **3 (Average quality):** Low quality randomized trials or well-designed non-randomized trials
- **2 (Low quality):** Case reports or clinical experience only
- **1 (Poor quality):** Little or no evidence

**[C]** Consistency of evidence refers to the degree to which the clinical trials addressing an intervention have consistent results. The scale used to measure consistency of evidence is:

- **5 (Highly consistent):** Multiple trials with similar outcomes
- **4 (Mainly consistent):** Multiple trials with some variability in outcome
- **3 (May be consistent):** Few trials or only trials with few patients; lower quality trials whether randomized or not
- **2 (Inconsistent):** Meaningful differences in direction of outcome between quality trials
- **1 (Anecdotal evidence only):** Evidence in humans based upon anecdotal experience

**[A]** Affordability refers to the overall cost of an intervention including drug cost, required supportive care, infusions, toxicity monitoring, management of toxicity, probability of care being delivered in the hospital, etc. with less expensive interventions being rated more highly than more expensive ones. The scale used to measure affordability is:

- **5 Very inexpensive**
- **4 Inexpensive**
- **3 Moderately expensive**
- **2 Expensive**
- **1 Very expensive**
### NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

<table>
<thead>
<tr>
<th>E</th>
<th>S</th>
<th>Q</th>
<th>C</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Efficacy of Regimen/Agent**

- **5 Highly effective:** Often provides long-term survival advantage or has curative potential
- **4 Very effective:** Sometimes provides long-term survival advantage or has curative potential
- **3 Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
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**Safety of Regimen/Agent**

- **5 Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLS)
- **4 Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLS
- **3 Mildly toxic:** Mild toxicity that interferes with ADLS is common
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**Quality of Evidence**

- **5 High quality:** Multiple well-designed randomized trials and/or meta-analyses
- **4 Good quality:** Several well-designed randomized trials
- **3 Average quality:** Low quality randomized trials or well-designed non-randomized trials
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**Consistency of Evidence**

- **5 Highly consistent:** Multiple trials with similar outcomes
- **4 Mainly consistent:** Multiple trials with some variability in outcome
- **3 May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
- **2 Inconsistent:** Meaningful differences in direction of outcome between quality trials
- **1 Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

**Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)**

- **5 Very inexpensive**
- **4 Inexpensive**
- **3 Moderately expensive**
- **2 Expensive**
- **1 Very expensive**
Chronic Myelogenous Leukemia

WORKUP

- H&P, including spleen size by palpation (cm below costal margin)
- CBC with differential, platelets
- Chemistry profile
- Bone marrow aspirate and biopsy
  - Morphologic review
    - Percent blasts
    - Percent basophils
  - Cytogenetics
    - FISH
- Quantitative RT-PCR (QPCR) using International Scale (IS)
- Determine risk score (See Risk Calculation Table CML-B)
- Human leukocyte antigen (HLA) testing, if considering allogeneic HCT

PH positive or BCR-ABL1 positive

Advanced phase CML

Ph negative and BCR-ABL1 negative

Evaluate for diseases other than CML (See Discussion)

Ph positive or BCR-ABL1 positive

Chronic phase CML

Discussion of treatment options including:
- Tyrosine kinase inhibitor (TKI)
- Role of HCT
- Clinical trial

Imatinib 400 mg QD (category 1)

or

Nilotinib 300 mg BID (category 1)

or

Dasatinib 100 mg QD (category 1)

See 3-Month Evaluation (CML-2)

See Discussion for additional information.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks, see page EB-1. All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>Smoldering (asymptomatic)(^{b,c,d,g})</th>
<th>Active (symptomatic)(^{b,e})</th>
</tr>
</thead>
</table>

### PRIMARY TREATMENT

<table>
<thead>
<tr>
<th>Smoldering (asymptomatic)(^{b,c,d,g})</th>
<th>Observe at 3- to 6-month intervals (category 1) or Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active (symptomatic)(^{b,e})</td>
<td>Myeloma therapy(^{h}) + bisphosphonates(^{i}) + adjunctive treatment(^{i}) as indicated</td>
</tr>
</tbody>
</table>

### FOLLOW-UP/SURVEILLANCE

| Smoldering (asymptomatic)\(^{b,c,d,g}\) | • Quantitative immunoglobulins + quantitation of M protein (serum and urine)  
• CBC, differential, platelet count  
• BUN, creatinine, corrected calcium  
• Bone survey annually or for symptoms  
• Bone marrow aspirate and biopsy as clinically indicated  
• Serum FLC assay as clinically indicated  
• MRI as clinically indicated  
• PET/CT scan as clinically indicated  
• Multi-parameter flow cytometry as clinically indicated |
|--------------------------------------|-------------------------------------------------------------|
| Active (symptomatic)\(^{b,e}\)       | • Quantitative immunoglobulins + quantitation of M protein (serum and urine)  
• CBC, differential, platelet count  
• BUN, creatinine, corrected calcium  
• Bone survey annually or for symptoms  
• Bone marrow aspirate and biopsy as clinically indicated  
• Serum FLC assay as clinically indicated  
• MRI as clinically indicated  
• PET/CT scan as clinically indicated |

### STAGE PROGRESSION

<table>
<thead>
<tr>
<th>Smoldering (asymptomatic)(^{b,c,d,g})</th>
<th>Progression to symptomatic myeloma(^{e})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active (symptomatic)(^{b,e})</td>
<td>See Active (Symptomatic) Myeloma below</td>
</tr>
</tbody>
</table>

### RESPONSE

<table>
<thead>
<tr>
<th>No response(^{f})</th>
<th>See Additional Treatment (MYEL-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem-cell harvest (adequate for 2 transplants), if candidate for transplantation (Refer for evaluation by stem cell transplant center)</td>
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</table>

### CLINICAL PRESENTATION

- See Staging Systems for Multiple Myeloma (MYEL-A).
- See Smoldering (Asymptomatic) Myeloma (MYEL-B).
- Includes Durie-Salmon Stage I Myeloma.
- See Active (Symptomatic) Myeloma (MYEL-B).
- See Response Criteria for Multiple Myeloma (MYEL-C).
- See Myeloma Therapy (MYEL-D).
- See Adjunctive Treatment (MYEL-E).

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Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

### Primary Therapy for Transplant Candidates

(Assess for response after 2 cycles)

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bortezomib/dexamethasone (category 1)</td>
<td>• Carfilzomib(^7)/lenalidomide(^4)/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dexamethasone</td>
<td>• Dexamethasone (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/doxorubicin/dexamethasone (category 1)</td>
<td>• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide(^4)/dexamethasone</td>
<td>• Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/thalidomide/dexamethasone (category 1)</td>
<td></td>
</tr>
<tr>
<td>• Lenalidomide(^4)/dexamethasone (category 1)</td>
<td></td>
</tr>
</tbody>
</table>

1Selected, but not inclusive of all regimens.
2Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
3Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
4Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
5Optimal dosing in this regimen has not been defined.

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