New Biologic Insights and Recent Therapeutic Advances in the Management of Acute and Chronic Leukemias and Myelodysplastic Syndromes

Proceedings from a Clinical Investigator Think Tank

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2 Audio CDs
New Biologic Insights and Recent Therapeutic Advances in the Management of Acute and Chronic Leukemias and Myelodysplastic Syndromes
A Continuing Medical Education Audio Program

OVERVIEW OF ACTIVITY
Hematologic cancers include the lymphomas, the leukemias, multiple myeloma and other related disorders (eg, myelodysplastic syndromes [MDS] and myeloproliferative disorders) stemming from lymphoid and myeloid progenitor cell lines. Taken together, it is estimated that approximately 163,000 new lymphoid, myeloid and leukemic cancer cases will be identified in the United States in the year 2015 and 54,000 individuals will die from these diseases. Although an extensive list of treatment options is available for these patients, this poses a challenge to the practicing physician who must maintain up-to-date knowledge of appropriate clinical management strategies across a vast spectrum of diseases. To address this issue, this CME program brings together leading clinical investigators to provide biologic insights into the recent therapeutic advances in the management of acute and chronic leukemias and MDS. By reviewing the available clinical trial data and relevant case scenarios, this initiative will provide perspectives on gaps in medical knowledge and highlight treatment ambiguities pertinent to the treatment of these diseases.

LEARNING OBJECTIVES
• Appraise recent data on therapeutic advances and changing practice standards in the management of select acute and chronic leukemias and MDS, and refine or validate existing treatment algorithms based on discussion of this information.
• Recognize evidence-based therapeutic options for patients with progressive chronic myeloid leukemia.
• Appreciate the FDA approvals of novel targeted agents indicated for the treatment of newly diagnosed and relapsed or refractory chronic lymphocytic leukemia, and discern how these treatments can be appropriately integrated into clinical practice.
• Review existing and evolving clinical trial data to recommend safe therapeutic alternatives for patients with acute myeloid leukemia, including acute promyelocytic leukemia, and increase knowledge regarding investigational options designed for patients who are not candidates for intensive therapy.
• Apply the results of emerging clinical research in osteoporosis treatment for young adult and adult patients with newly diagnosed and recurrent acute lymphoblastic leukemia.
• Counsel patients with MDS about supportive and systemic treatment options to manage disease-related cytopenias and minimize leukemic progression.

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FACULTY — Dr Kantarjian has no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: Dr Brown — Advisory Committee: Celgene Corporation, Emergent BioSolutions Inc, Gilead Sciences Inc, Janssen Biotech Inc, MorphoSys, Pharmacys Inc, ProNAi Therapeutics Inc; Consulting Agreements: Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Emergent BioSolutions Inc, Genentech BioOncology, Gilead Sciences Inc, GlaxoSmithKline, Janssen Biotech Inc, MorphoSys, Pharmacys Inc, ProNAi Therapeutics Inc, Roche Laboratories Inc. Dr Schiffer — Advisory Committee: Boehringer Ingelheim Pharmaceuticals Inc, Eisai Inc, Novartis Pharmaceuticals Corporation, Takeda Oncology; Consulting Agreement: Celgene Corporation; Contracted Research: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Takeda Oncology, Research Support: MedImmune Inc; Other Remunerated Activities: Pfizer Inc, Takeda Oncology. Dr Smith — Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc. Dr Steensma — Advisory Committee: Amgen Inc, Celgene Corporation, Genoptix Inc. Dr Stock — Advisory Committee: Amgen Inc, Gilead Sciences Inc, Sigma-Tau Pharmaceuticals Inc.

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RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

Visit www.ResearchToPractice.com/LeukemiaTT115/Video to access a number of short video highlight segments and corresponding text transcripts from the Think Tank proceedings featuring discussion of key clinical and research issues focused on the management of acute and chronic leukemias and myelodysplastic syndromes.
Track 1 Case discussion: A 65-year-old man with high-risk chronic lymphocytic leukemia (CLL) requiring treatment for progressively worsening cytopenias and lymphadenopathy

Track 2 Treatment for younger versus older patients with newly diagnosed high-risk CLL

Track 3 Phase Ib study of obinutuzumab with fludarabine/cyclophosphamide or bendamustine as initial therapy for CLL

Track 4 Potential role of lenalidomide in the treatment of CLL

Track 5 Investigation of rituximab or ofatumumab as maintenance therapy for CLL

Track 6 Clinical implications of the CLL11 trial of obinutuzumab/chlorambucil in patients with CLL and comorbidities

Track 7 Activity and clinical use of ibrutinib for relapsed or refractory CLL

Track 8 Incidence of ibrutinib-associated side effects

Track 9 Case discussion: A 64-year-old woman with del(11q) CLL receives idelalisib after disease progression on multiple treatment regimens

Track 10 Management of idelalisib-associated side effects

Track 11 Activity and tolerability of idelalisib/rituximab in patients aged 65 or older with treatment-naïve CLL

Track 12 Clinical experience with the Bcl-2 inhibitor venetoclax (ABT-199) as treatment for relapsed/refractory CLL

Track 13 Key issues and controversies in the management of chronic myelogenous leukemia (CML)

Track 14 Case discussion: A 29-year-old man with chronic-phase CML has not yet achieved a major molecular response after 1 year of initial therapy with nilotinib

Track 15 Selection of nilotinib, dasatinib or imatinib as initial therapy for patients with CML

Track 16 Considerations for changing tyrosine kinase inhibitor (TKI) therapy in patients who have not achieved a major molecular response

Track 17 Perspectives on continuation of TKI therapy for patients with CML who wish to conceive children

Track 18 Case discussion: A 56-year-old man with low- to intermediate-risk CML develops pleural effusions during treatment with dasatinib

Track 19 Management of TKI-associated pleural effusion

Track 20 Mechanism of action of the protein synthesis inhibitor omacetaxine mepesuccinate

Track 21 Clinical experience with omacetaxine mepesuccinate for patients with CML
Track 22 SORAML: Results of a Phase II trial of sorafenib versus placebo in addition to standard therapy for younger patients with newly diagnosed acute myeloid leukemia (AML)

Track 23 Activity of sorafenib in patients with FLT3-ITD mutation-negative versus FLT3-ITD mutation-positive AML

Track 24 Efficacy of azacitidine as treatment for elderly patients with AML

Track 25 Recent clinical data with the polo-like kinase inhibitor volasertib in elderly patients with AML

Track 26 Case discussion: A 65-year-old woman presenting with hemiparesis and an unusually high white blood cell count is diagnosed with acute promyelocytic leukemia (APL)

Track 27 Options for initial therapy in APL

Track 28 Activity of all-trans retinoic acid in combination with arsenic trioxide in APL

Track 29 Clinical landscape of emerging research in myelodysplastic syndromes (MDS)

Track 30 Case discussion: A 77-year-old woman is diagnosed with intermediate-risk MDS after presenting with pancytopenia and fatigue

Track 31 Choice between azacitidine and decitabine as initial therapy and consideration of allogeneic stem cell transplant in patients with intermediate-risk MDS

Track 32 Management of azacitidine-associated cytopenias

Track 33 Investigational options for patients with MDS progressing on azacitidine

Track 34 Results of a Phase III study of lenalidomide versus placebo in red blood cell transfusion-dependent patients with low- to intermediate-risk MDS without del(5q) and unresponsive or refractory to erythropoiesis-stimulating agents

Track 35 Clinical management of acute lymphoblastic leukemia (ALL) in the community compared to tertiary care settings

Track 36 Comparison of adult and pediatric treatment regimens for ALL and use of pediatric regimens in the adult population

Track 37 Benefits and risks associated with the inclusion of asparaginase in treatment regimens for ALL

Track 38 Mechanism of action and historical development of asparaginase in ALL

Track 39 Clinical experience with different preparations of asparaginase in ALL

Track 40 Benefits of the Erwinia-based preparation of asparaginase

Track 41 Emerging data with the monoclonal antibody blinatumomab as treatment for ALL

Track 42 ECOG-E1910: An ongoing Phase III trial of chemotherapy with or without blinatumomab for adult patients with newly diagnosed BCR-ABL-negative B-lineage ALL

Track 43 Magnitude of clinical responses observed with chimeric antigen receptor T-cell therapy in ALL
SELECT PUBLICATIONS


Cortes JE et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: Results with 24 months of follow-up. *Cancer* 2015;121(10):1637-44.


Döhner H et al. Randomized, phase 2 trial of low-dose cytarabine with or without volasertib in AML patients not suitable for induction therapy. *Blood* 2014;124(9):1426-33.


Grupp SA et al. T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) have long term persistence and induce durable remissions in children with relapsed, refractory ALL. *Proc ASH* 2014; Abstract 380.


Park JH et al. CD19-targeted 19-28z CAR modified autologous T cells induce high rates of complete remission and durable responses in adult patients with relapsed, refractory B–cell ALL. *Proc ASH* 2014; Abstract 382.


Sanitini V et al. Efficacy and safety of lenalidomide versus placebo in RBC-transfusion dependent patients with IPSS low/intermediate (int–1)–risk myelodysplastic syndromes without del(5q) and unresponsive or refractory to erythropoiesis-stimulating agents: Results from a randomized phase 3 study (CC–5013–MDS–005). *Proc ASH* 2014; Abstract 409.


QUESTIONS (PLEASE CIRCLE ANSWER):

1. Which of the following agents approved for the treatment of CML is classified as a protein synthesis inhibitor?
   a. Bosutinib  
   b. Dasatinib  
   c. Omacetaxine mepesuccinate  
   d. Ponatinib  
   e. All of the above

2. Which of the following is an adverse event associated with idelalisib treatment in patients with CLL?
   a. Transaminitis  
   b. Pneumonitis  
   c. Colitis  
   d. Both a and b  
   e. All of the above

3. The achievement of partial responses with lymphocytosis in patients with CLL may be observed as part of the clinical pattern of response associated with _____________ treatment.
   a. Single-agent idelalisib  
   b. Single-agent ibrutinib  
   c. Both a and b

4. Lenalidomide therapy did not result in improved rates of transfusion independence when compared to placebo in patients with low/intermediate-risk MDS without del(5q) who were unresponsive or refractory to erythropoiesis-stimulating agents.
   a. True  
   b. False

5. Initial management of high-risk APL (high white blood cell count, bleeding complications) should include _____________.
   a. All-trans retinoic acid  
   b. Steroids  
   c. Anthracycline  
   d. All of the above

6. Data from the Phase II SORAML study indicate that clinical benefit with the addition of sorafenib to standard therapy in younger patients with newly diagnosed AML was restricted to only those with FLT3-ITD mutation-positive disease.
   a. True  
   b. False

7. In elderly patients with AML who were unfit for intensive induction therapy, the addition of volasertib, a polo-like kinase inhibitor, to low-dose cytarabine improved efficacy in terms of _____________ when compared to low-dose cytarabine alone.
   a. Response rate  
   b. Median event-free survival  
   c. Median overall survival  
   d. Both b and c  
   e. All of the above

8. Which of the following is the mechanism of action of venetoclax (ABT-199)?
   a. Bcl-2 inhibitor  
   b. FLT3 inhibitor  
   c. Protein synthesis inhibitor

9. Intensive treatment regimens developed for pediatric patients with ALL have also been shown to be efficacious for the treatment of older adolescents and young adults with this disease.
   a. True  
   b. False

10. In adults with relapsed/refractory ALL, the bispecific T-cell engaging monoclonal antibody ____________ resulted in high complete remission rates.
     a. Obinutuzumab  
     b. Blinatumomab  
     c. Ofatumumab
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PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent       3 = Good       2 = Adequate       1 = Suboptimal

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<td>Results of the Phase III MDS-005 trial evaluating lenalidomide in patients with transfusion-dependent, lower-risk MDS without del(5q)</td>
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<td>Benefits of the Erwinia-based preparation of asparaginase for patients with ALL</td>
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Practice Setting:
- ☐ Academic center/medical school
- ☐ Community cancer center/hospital
- ☐ Group practice
- ☐ Solo practice
- ☐ Government (eg, VA)
- ☐ Other (please specify)

Was the activity evidence based, fair, balanced and free from commercial bias?
- ☐ Yes
- ☐ No
- ☐ If no, please explain:

Please identify how you will change your practice as a result of completing this activity (select all that apply).
- ☐ This activity validated my current practice
- ☐ Create/revise protocols, policies and/or procedures
- ☐ Change the management and/or treatment of my patients
- ☐ Other (please explain):

If you intend to implement any changes in your practice, please provide 1 or more examples:

The content of this activity matched my current (or potential) scope of practice.
- ☐ Yes
- ☐ No
- ☐ If no, please explain:

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes   3 = Will consider   2 = No   1 = Already doing   N/M = LO not met   N/A = Not applicable

As a result of this activity, I will be able to:

- Appraise recent data on therapeutic advances and changing practice standards in the management of selective acute and chronic leukemias and MDS, and refine or validate existing treatment algorithms based on discussion of this information
- Recognize evidence-based therapeutic options for patients with progressive chronic myeloid leukemia
- Appreciate the FDA approvals of novel targeted agents indicated for the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia, and discern how these treatments can be appropriately integrated into clinical practice
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EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

As a result of this activity, I will be able to:

- Apply the results of emerging clinical research to optimize treatment for young adult and adult patients with newly diagnosed and recurrent acute lymphoblastic leukemia.
- Counsel patients with MDS about supportive and systemic treatment options to manage disease-related cytopenias and minimize leukemic progression.

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

Would you recommend this activity to a colleague?
- Yes
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- Yes, I am willing to participate in a follow-up survey.
- No, I am not willing to participate in a follow-up survey.

PART 2 — Please tell us about the faculty and moderator for this educational activity

<table>
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<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
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<tr>
<td>Jennifer R Brown, MD, PhD</td>
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<td>Neil Love, MD</td>
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Please recommend additional faculty for future activities:

REQUEST FOR CREDIT — Please print clearly

Name: ________________________________ Specialty: ________________________________

Professional Designation:
- [ ] MD  [ ] DO  [ ] PharmD  [ ] NP  [ ] RN  [ ] PA  [ ] Other

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