Chapter 17

CURRENT TREATMENT OF ACUTE MYELOID LEUKEMIA

Selin Merih URLU[1]

INTRODUCTION

The syndrome of acute myeloid leukemia (AML) includes a heterogenous group of cancers of blood cells that arise from clonal expansion of malignant hematopoietic precursor cells. Acute myeloid leukemia is the most frequent acute leukemia of adults and has an unfavorable prognosis (Schiffer&Anastasi, 2014). Recent advances in acute myeloid leukemia biology and its genetic landscape should ultimately lead to more subset specific AML therapies, ideally tailored to each patient's disease. Although a growing number of distinct AML subsets have been increasingly characterized, patient management has remained disappointingly uniform (Dombret&Gardin, 2016).The WHO continues to define specific acute myeloid leukemia disease entities by focusing on significant cytogenetic and moleculargenetic subgroups. If one excludes acute promyelocytic leukemia, current AML management still relies largely on intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT). Core therapy for AML has remained unchanged for nearly 30 years and survival rates remain unsatisfactory. Mutational profiling has fundamentally changed our approach to patients with acute myeloid leukemia. However, advances in the immunotherapy of AML have created opportunities for improved outcomes. In the last 2 years, at least 5 new treatments for acute myeloid leukemia have become more widely available: CPX-351, a liposomal form of daunorubicin and cytarabine; midostaurin, a multikinase inhibitor with potency against AML with mutations in the FMS-like tyrosine kinase 3 (FLT3) gene; gemtuzumab ozagomicin (GO), the humanized monoclonal antibody-drug conjugate; and enasidenib and ivosidenib, oral inhibitors of isocitrate dehydrogenase-2 (IDH2) and IDH1, respectively (Michaelis, 2018).

In the last decade with the identification of molecular genetic disorders involved in the pathogenesis of AML; it is possible to confirm the diagnosis, to determine the prognosis and to develop treatment options for these goals.In this article we will discuss the current management of acute myeloid leukemia.

[1] HematolojiUzmanı, Ankara NumuneEğitimveAraştırmaHastanesi, smerihoz@gmail.com

with azacitidine, decitabine, or low dose cytarabine. Venetoclax was approved by the FDA for use in combination with low dose cytarabine or a hypomethylating agent in newly diagnosed AML in patients ≥75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy (Larson &Schmader, 2017).

Targeted immunotherapy: A variety of therapeutic antibodies directed against AML antigenic targets (eg, CD33, CD123, CLEC12A), bispecific T-cell engagers, or dual-affinity retargeting molecules as well as engineered chimericantigen receptor T cells targeting the CD33 and CD123 antigens are currently in early clinical trial (Döhner et al., 2017).

CONCLUSION

The current standard of care for the treatment of adults with AML remains suboptimal. Scientific advances are helping better understand the biological differences among different patients' leukemias and identifying potential targets for novel therapies. So it should be become mandatory to routinely molecularly characterize cases of newly diagnosed AML to identify these targets before therapy.

REFERENCES

Arber, D. A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M. J., Le Beau, M. M., ...&Vardiman, J. W. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood, 127(20), 2391-2405.

Bixby, D. L., Stein, A. S., Fathi, A. T., Kovacsovics, T. J., Levy, M. Y., Erba, H. P., ... & Stein, E. M. (2016). Vadastuximabtalirinemonotherapy in older patients with treatment naive CD33-positive acute myeloid leukemia (AML).

Burnett, A. K., Russell, N. H., Hills, R. K., Hunter, A. E., Kjeldsen, L., Yin, J., ... & Milligan, D. (2013). Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. Journal of clinical oncology, 31(27), 3360-3368.

Burnett, A. K., Russell, N. H., Hills, R. K., Kell, J., Cavenagh, J., Kjeldsen, L., ... & Thomas, I. F. (2015). A randomised comparison of daunorubicin 90mg/m 2 vs 60mg/m 2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. Blood, blood-2015.

Cornelissen, J. J., van Putten, W. L., Verdonck, L. F., Theobald, M., Jacky, E., Daenen, S. M., ... & van der Lelie, H. (2007). Myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle aged adults: benefits for whom? results of a HOVON/SAKK donor versus no donor analysis. Blood.

Cortes, J. E., Goldberg, S. L., Feldman, E. J., Rizzeri, D. A., Hogge, D. E., Larson, M., ... &Kantarjian, H. (2015). Phase II, multicenter, randomized trial of CPX-351 (cytarabine: daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. Cancer, 121(2), 234-242.

Dombret, H., &Gardin, C. (2016).An update of current treatments for adult acute myeloid leukemia. Blood, 127(1), 53-61.

Döhner, H., Estey, E. H., Amadori, S., Appelbaum, F. R., Büchner, T., Burnett, A. K., ...& Lo-Coco, F. (2010). Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood, 115(3), 453-474.

Döhner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F. R., Büchner, T., ...& Levine, R. L. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood, 129(4), 424-447.

Fernandez, H. F., Sun, Z., Yao, X., Litzow, M. R., Luger, S. M., Paietta, E. M., ...& Rowe, J. M. (2009). Anthracycline dose intensification in acute myeloid leukemia. New England Journal of Medicine, 361(13), 1249-1259.

Giles, F. J., Borthakur, G., Ravandi, F., Faderl, S., Verstovsek, S., Thomas, D., ...&Albitar, M. (2007). The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. British journal of haematology, 136(4), 624-627.

Grimwade, D., Hills, R. K., Moorman, A. V., Walker, H., Chatters, S., Goldstone, A. H., ... & National Cancer Research Institute Adult Leukaemia Working Group. (2010). Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood, 116(3), 354-365.

Hills, R. K., Castaigne, S., Appelbaum, F. R., Delaunay, J., Petersdorf, S., Othus, M., ...& Cahn, J. Y. (2014). Addition of gemtuzumabozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. The lancet oncology, 15(9), 986-996.

Kadia, T. M., Ravandi, F., Cortes, J., &Kantarjian, H. (2016).New drugs in acute myeloid leukemia. Annals of Oncology, 27(5), 770-778.

Lambert, J., Pautas, C., Terré, C., Raffoux, E., Turlure, P., Caillot, D., ...& Rubin, S. D. (2019). Gemtuzumabozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. haematologica, 104(1), 113-119.

Lancet, J. E., Uy, G. L., Cortes, J. E., Newell, L. F., Lin, T. L., Ritchie, E. K., ... & Stone, R. M. (2016). Final results of a phase III randomized trial of CPX-351 versus 7+ 3 in older patients with newly diagnosed high risk (secondary) AML.

Larson, R. A., Lowenberg, B., & Connor, R. F. (2013).Induction therapy for acute myeloid leukemia in younger adults.UpToDate: Waltham, MA.

Larson, R. A. (2015). Post-remission therapy for acute myeloid leukemia in younger adults.Up to Date, 18.

Larson, R. A., Mandrekar, S. J., Sanford, B. L., Laumann, K., Geyer, S. M., Bloomfield, C. D., ... & Coco, F. L. (2017). An analysis of maintenance therapy and post-midostaurin outcomes in the international prospective randomized, placebo-controlled, double-blind trial (CALGB 10603/RATIFY [alliance]) for newly diagnosed acute Myeloid leukemia (AML) patients with FLT3 mutations.

Larson, R. A., &Schmader, K. E. (2017). Acute myeloid leukemia: treatment and outcomes in older adults. UpToDate. Waltham, MA: UpToDate.

Lazarus, H. M., Pérez, W. S., Klein, J. P., Kollman, C., Bate-Boyle, B., Bredeson, C. N.,

...& Marks, D. I. (2006). Autotransplantation versus HLA-matched unrelated donor transplantation for acute myeloid leukaemia: a retrospective analysis from the Center for International Blood and Marrow Transplant Research. British journal of haematology, 132(6), 755-769.

Löwenberg, B. (2013). Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. Blood, 121(1), 26-28.

Luskin, M. R., Lee, J. W., Fernandez, H. F., Abdel-Wahab, O., Bennett, J. M., Ketterling, R. P., ... & Patel, J. P. (2016). Benefit of high dose daunorubicin in AML induction extends across cytogenetic and molecular groups: updated analysis of E1900. Blood, blood-2015.

Michaelis, L. C. (2018). Cytotoxic therapy in acute myeloid leukemia: not quite dead yet. ASH Education Program Book, 2018(1), 51-62.

Novotny-Diermayr, V., Hart, S., Goh, K. C., Cheong, A., Ong, L. C., Hentze, H., ...& Wood, J. M. (2012). The oral HDAC inhibitor pracinostat (SB939) is efficacious and synergistic with the JAK2 inhibitor pacritinib (SB1518) in preclinical models of AML. Blood cancer journal, 2(5), e69.

O'Donnell, M. R., Tallman, M. S., Abboud, C. N., Altman, J. K., Appelbaum, F. R., Arber, D. A., ... & De Lima, M. (2017). Acute myeloid leukemia, version 3.2017, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network, 15(7), 926-957.

Pautas, C., Merabet, F., Thomas, X., Raffoux, E., Gardin, C., Corm, S., ...& De Revel, T. (2010). Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. Journal of Clinical Oncology, 28(5), 808-814.

Pollyea, D. A. (2018).New drugs for acute myeloid leukemia inspired by genomics and when to use them. ASH Education Program Book, 2018(1), 45-50.

Ravandi, F., Ritchie, E. K., Sayar, H., Lancet, J. E., Craig, M. D., Vey, N., ...&Pigneux, A. (2015). Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomised, controlled, double-blind, multinational, phase 3 study. The lancet oncology, 16(9), 1025-1036.

Roloff, G. W., & Griffiths, E. A. (2018).When to obtain genomic data in acute myeloid leukemia (AML) and which mutations matter.Blood advances, 2(21), 3070-3080.

Schiffer, C. A., &Anastasi, J. (2014).Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia.Up to Date, 20119.

Schiffer, C. A., Larson, R. A., & Connor, R. F. (2017).Prognosis of acute myeloid leukemia.UpToDate. Waltham, MA: UpToDate.

Schmid, C., Labopin, M., Socié, G., Daguindau, E., Volin, L., Huynh, A., ...&Maertens, J. (2015). Outcome of patients with distinct molecular genotypes and cytogenetically normal AML after allogeneic transplantation. Blood, 126(17), 2062-2069.

Sutherland, M. S. K., Walter, R. B., Jeffrey, S. C., Burke, P. J., Yu, C., Kostner, H., ... &Zeng, W. (2013). SGN-CD33A: a novel CD33-targeting antibody-drug conjugate utilizing a pyrrolobenzodiazepine dimer is active in models of drug-resistant AML. Blood, blood-2013.

Stone, R. M., Mandrekar, S. J., Sanford, B. L., Laumann, K., Geyer, S., Bloomfield, C. D., ...& Lo-Coco, F. (2017). Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. New England Journal of Medicine, 377(5), 454-464.