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How I treat acute myeloid leukemia presenting with preexisting comorbidities

Yishai Ofran,[1,2] Martin S. Tallman,[3,4] and Jacob M. Rowe[1,2,5]

[1]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel; [2]Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel; [3]Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY; [4]Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY; and [5]Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel

Acute myeloid leukemia (AML) is a devastating disease with an incidence that progressively increases with advancing age. Currently, only ~40% of younger and 10% of older adults are long-term survivors. If untreated, the overall prognosis of AML remains dismal. Initiation of therapy at diagnosis is usually urgent. Barriers to successful therapy for AML are the attendant toxicities directly related to chemotherapy or those associated with inevitable aplasia. Organ dysfunction often further complicates such toxicities and may even be prohibitive. There are few guidelines to manage such patients and the fear of crossing the medico-legal abyss may dominate. Such clinical scenarios provide particular challenges and require experience for optimal management. Herein, we discuss select examples of common pretreatment comorbidities, including cardiomyopathy, ischemic heart disease; chronic renal failure, with and without dialysis; hepatitis and cirrhosis; chronic pulmonary insufficiency; and cerebral vascular disease. These comorbidities usually render patients ineligible for clinical trials and enormous uncertainty regarding management reigns, often to the point of withholding definitive therapy. The scenarios described herein emphasize that with appropriate subspecialty support, many AML patients with comorbidities can undergo therapy with curative intent and achieve successful long-term outcome. (*Blood*. 2016;128(4):488-496)

Introduction

Although the initial therapy of acute myeloid leukemia (AML) has been standardized and forms the backbone of clinical trials, many patients do not receive conventional therapy at diagnosis due to existing or potential comorbidities which cause much anxiety among patients and clinicians. Herein, we present 8 selective, but common, clinical vignettes describing, with subspecialty advice, a pragmatic approach to the management of patients with AML who present with varying degrees of organ dysfunction. Adhering whenever possible to standard therapy had been the guiding principle in suggesting the optimal antileukemic therapy.[1] The primary focus is on induction and consolidation with only general reference to allogeneic transplantation.

Scenario 1: patient with cardiomyopathy

A 57-year old man was admitted with a 2-week history of generalized weakness and mild dyspnea. He was found to have intermediate-risk AML (normal karyotype, no nucleophosmin [NPM1], CCAAT/enhancer-binding protein [CEBPA], or *Fms-related tyrosine kinase 3* [*FLT3*]–internal tandem duplication [ITD] mutations identified). His past medical history is remarkable for ischemic heart disease with a myocardial infarction 11 months prior to admission. Otherwise, he was in good health. On admission, his white blood cell count was 43×10^9/L, with 91% blasts, hemoglobin 7.8 g/dL with platelets 22×10^9/L. The bone marrow (BM) was diffusely infiltrated with blast cells. He was afebrile with a normal chest radiograph. The echocardiogram revealed mildly reduced left ventricular systolic function with an ejection fraction (LVEF) of 42%.

Questions

Can standard induction and consolidation therapy be given to this patient with cardiomyopathy and, if not, what are the alternatives?
Can such a patient undergo allogeneic transplantation?
What is the best way to monitor the cardiac disease?
Is there a role for cardioprotective agents?

Cardiac dysfunction in newly diagnosed patients with AML is not an uncommon problem encountered in practice, particularly among older patients. This is even more relevant in the current era when standard induction therapy is given to an ever increasing older population. As anthracyclines form the core of induction therapy in AML, any cardiac dysfunction may limit the optimal treatment that can be given.

Several issues need to be considered. First, the most common approach to monitor cardiac function is the evaluation of LVEF. Radionuclide angiography measuring multigated blood pool imaging (multigated acquisition scan) or echocardiography (preferably, 3-dimensional) are commonly used. For added accuracy in marginal cases, as in this patient, measurement of LVEF by magnetic resonance imaging is considered by many to be the gold standard.[2] However, we do not incorporate it into routine clinical practice. In general, because of the potential for progressive toxicity in a patient with cardiomyopathy, a LVEF of 45% as the threshold for using anthracyclines in the treatment of AML has been suggested[3,4] (Table 1). Although such a cutoff is necessarily arbitrary, it is the most commonly used value for eligibility to large cooperative oncology group clinical trials in AML. Given the need to optimize the therapy in AML and being fully cognizant of the risk/benefit considerations, it may be entirely reasonable to offer standard induction therapy with very close cardiac monitoring. The

Submitted January 24, 2016; accepted May 18, 2016. Prepublished online as *Blood* First Edition paper, May 27, 2016; DOI 10.1182/blood-2016-01-635060.

Table 1. Select precautions and recommendation for AML therapy in patients with heart disease

	Specific supportive care considerations	Induction therapy	Postremission strategy
LVEF <45%[3,4]	1. Minimize IV infusions 2. Repeat LVEF evaluation prior to each chemotherapy cycle	1. HiDAC or 7+3 2. If anthracycline used, consider epirubicin or mitoxantrone	1. Repeated HiDAC 2. RIC allo-SCT may be considered for high-risk AML
Ischemic heart disease[15,17]	1. Aspirin + beta-blocker 2. Maintain hemoglobin >8 g/dL	1. If possible, postpone induction for few days 2. Use HiDAC 3. Avoid anthracycline 4. Aspirin throughout induction	Based on leukemia risk stratification and LVEF
	1. PCI prior to induction if active ischemia despite maximal noninvasive therapy 2. Bare metal stent		If not performed prior to induction, PCI is indicated for pending coronary obstruction prior to chemotherapy

allo-SCT, allogeneic stem cell transplantation.

choice is very individualized and will take into account the patient's age, performance status, and any comorbidities.

There are also alternative therapeutic options. One approach would be to avoid anthracyclines and offer this patient induction with high-dose cytarabine at doses that are adjusted for his age. Although several dosing options can be considered, our own preference, based on published experience, is a dose of 1.5 g/m^2 given over 1 hour twice daily for 6 days.[5] Gemtuzumab ozogamicin has also been used as a substitute for daunorubicin,[6] although this is currently unavailable in much of the world. An amsacrine-based regimen has also been proposed,[7] but this is not commonly used nowadays.

Several methods have been reported to potentially reduce the risk of progressive toxicity from anthracyclines.[8] These include infusional administration of anthracyclines, or the use of the anthracenedione, mitoxantrone.[9-12] Liposomal encapsulation, in various formulations, has been suggested to reduce cardiotoxicity,[13] but there are no compelling data to support such a recommendation. There has been considerable discussion about the use of dexrazoxane as a chelator that may prevent anthracycline damage by binding to free iron radicals. Given the theoretic risk of retarding the desired clinical benefit, outside of a clinical trial we do not recommend any of these strategies.[14,15] Impairment of heart function may restrict standard supportive measures during induction such as antibiotics, transfusions, and electrolyte replacement that are associated with large fluid volumes.

If this patient achieves complete remission with high-dose cytarabine, we would recommend offering postremission therapy with 2 additional cycles of the same regimen.[5] Irrespective of the agent used, close ongoing cardiac monitoring remains essential.

The possibility of allogeneic transplantation in such patients is more complex than induction or consolidation therapy, mainly because of the prolonged immune suppression with its attendant complications. However, if the genetic prognostic factors are such that the graft-versus-leukemia effect is considered an essential component for curative therapy, a reduced-intensity conditioning (RIC) allogeneic transplantation can be judiciously considered with very close cardiac monitoring.

Comment

Overall, the outlook for patients with cardiomyopathy, if clinically stable, need not preclude therapy for AML.

Scenario 2: patient with ACS

A 45-year-old man presented with new onset of chest pain and anemia. Cardiac computerized tomography revealed normal systolic function, but with significant narrowing of the right coronary artery (Figure 1). Acute coronary syndrome (ACS) was diagnosed. The white blood count was 10×10^9/L with 20% blasts. BM aspiration and biopsy were diagnostic for AML, molecularly characterized with normal cytogenetics and NPM1, as the only identified mutation.

Questions

Is the treatment of AML feasible in the setting of ACS?
What is the optimal antiplatelet therapy?
Should coronary intervention precede induction?

The combination of ACS and AML presents an unusually complicated predicament. For this patient, immediate medical therapy should include the combination of aspirin, beta-blockers,[16,17] allopurinol, hydration, correction of electrolyte imbalances, and maintenance of hemoglobin level of 8 g/dL.[18] Hydroxyurea is indicated for a rapidly increasing blast count. If ischemic symptoms subside, we would monitor the patient without initiating induction therapy for 5 to 7 days. If the patient remains stable and without symptoms, induction of remission is warranted.[19] Although the patient presents with a normal cardiac function, active coronary disease increases the risk for anthracycline toxicity.[15] This risk needs to be balanced against the importance of using anthracyclines for remission induction. Therefore, either 3+7 with standard anthracycline doses or high-dose cytarabine is a reasonable option for induction.[20]

Aspirin is the drug of choice for ACS[21] and reduces progression to myocardial infarction or death in 30 days from 13.4% to 4.2%.[22] Therefore, although there are no established guidelines in this setting, we recommend aspirin throughout induction while attempting to maintain, arbitrarily, the platelet count above 30×10^9/L. The addition

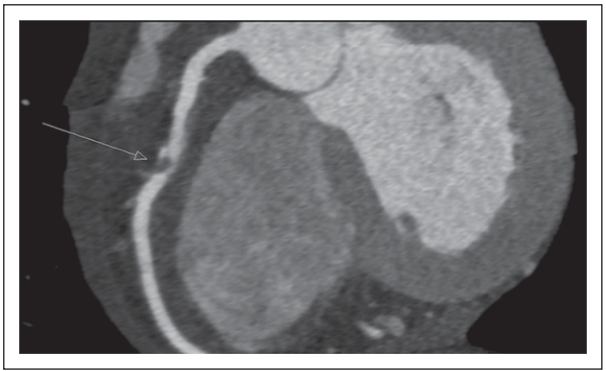

Figure 1. Coronary computerized tomography demonstrating atherosclerotic occlusion of the right coronary artery.

of anticoagulation, or other antiplatelet agents, may further modestly reduce the death risk; however, such practice increases the risk of bleeding and should be avoided.

For this patient, if signs or symptoms of ischemia persist, percutaneous coronary intervention (PCI) should be discussed. Intractable ischemia must be resolved prior to initiating induction therapy. The risks of progression to myocardial infarction, life-threatening arrhythmia, and sudden death are increased with stress, electrolyte imbalance, and hypoxia, all common during induction. Therefore, it is suggested that if symptoms of ischemia persist despite optimal medical therapy, revascularization should precede induction therapy. Following PCI, dual antiplatelet therapy is indicated to minimize the risk of stent thrombosis. In most patients with AML, induction should not be significantly delayed. Therefore, implantation of a drug-eluting stent that requires longer duration of dual antiplatelet therapy should be avoided if possible. Because the risk of stent thrombosis peaks during the first 14 days after PCI, and with bare-metal stent decreases thereafter, clopidogrel discontinuation should be considered 14 days after PCI to coincide with the development of induction-related severe thrombocytopenia.

Comment

Overall, the presence of ACS should not discourage aggressive therapy for AML.

Scenario 3: patient with newly diagnosed AML

A 55-year-old woman presents with newly diagnosed AML. Biallelic mutation in CEBPA is detected with a normal karyotype. She has a history of diabetes mellitus and diabetic nephropathy with chronic renal failure and a creatinine of 3.0 mg/dL, but does not require dialysis.

Questions

What precautions are necessary?
What is the best approach to induction and postremission therapy?
Are there required chemotherapy dose adjustments?

The treatment of a patient with newly diagnosed AML and chronic renal failure presents several challenges. A joint effort between the hematologist and nephrologist is required. The earliest issue which needs attention is the potential for tumor lysis syndrome (TLS). An elevated pretreatment serum creatinine >1.4 mg/dL is an independent risk factor for the development of both laboratory and clinical TLS.[23] In cases of severe TLS, leukapheresis may be considered, even at leukocyte levels lower than the standard threshold for leukapheresis.[24] In a patient with impaired renal function, intensive fluid administration needs to be carefully monitored to avoid fluid overload or volume depletion. We use loop diuretics to increase urine flow rate. The administration of sodium bicarbonate is no longer generally recommended.[25] Moreover, in patients with severe renal failure it is contraindicated because of concern for metabolic alkalosis that may develop due to the retention of sodium bicarbonate. Allopurinol can be administered in doses adjusted for the degree of renal function.[26] Rasburicase may be used if needed.

The best approach to induction and postremission therapy in a patient with chronic renal failure is unknown. Because cytarabine is generally metabolized by liver cytidine deaminase, dose reduction is not required when standard doses (<400 mg/m^2 per day) are administered.[27] However, when higher doses are given (2-3 g/m^2) to patients with renal dysfunction, neurotoxicity has been observed.[28] In a study of 110 patients with AML given high-dose cytarabine, among patients with estimated creatinine clearance <60 mL per minute, 76% were complicated by neurotoxicity compared with 8% of those with creatinine clearance >60 mL per minute.[28] The recommended dose adjustments are as follows: if the creatinine clearance is 46 to 60 mL per minute, administer 60% of the dose; if the creatinine clearance is 31 to 45 mL per minute, administer 50% of the total dose; and if the creatinine clearance is <30 mL per minute, consider an alternative agent[29] (Table 2). However, despite such an elegant algorithm, given the concerns of neurotoxicity (admittedly often reversible[28]) and hepatotoxicity, we do not administer high-dose cytarabine to patients with renal impairment. We maintain this practice even among patients with core-binding factor AML for whom it has been suggested that high-dose cytarabine may be particularly effective in prolonging survival.[30]

The anthracyclines are primarily eliminated by renal and hepatic aldoketo reductase and biliary excretion. Less than 20% is eliminated in the urine.[27] Of all anthracyclines, pharmacokinetic data are most robust for doxorubicin.[31] Yet, there are no consistent recommendations regarding the need for dose reduction.[32-34] Among anthracyclines, daunorubicin has the greatest fractional renal clearance, and we follow the common recommendation to reduce the dose by 50% for a creatinine >3 mg/dL.[32]

With dose reduction for anthracyclines and standard-dose cytarabine (100 mg/m^2 per day for 7 days by continuous induction), such conventional induction chemotherapy can be administered even to patients with very low creatinine clearance. As consolidation, one could give the identical induction regimen, but we would use the combination of mitoxantrone plus etoposide. The dose of mitoxantrone does not require adjustment.[32,35,36] Etoposide is primarily eliminated by the liver and kidney, but pharmacokinetics are apparently the same in patients with end-stage renal disease as in normal individuals.[37] Therefore, dose modifications are regarded as empiric. We adjust the dose and administer 75% of the total dose if the creatinine clearance is 10 to 50 mL per minute and give 50% of the dose if the creatinine clearance is <10 mL per minute.[29]

Scenario 4: patient with renal dysfunction

What if a patient on chronic dialysis presents with AML?

Questions

Is AML therapy feasible in patients on chronic dialysis?
Should the goals of AML therapy be altered because of kidney disease?
What chemotherapy regimens can be safely administered?

Considerations related to impaired renal function, as outlined above, also apply to patients on chronic dialysis (Table 2). Ironically, hemodialysis is an effective treatment of intractable fluid overload, hyperkalemia, hyperuricemia, hyperphosphatemia, or hypocalcemia[38] and its frequency can be adjusted to prevent life-threatening electrolyte abnormalities.

Awareness and rapid response to early signs of infections are of particular importance, because life-threatening infections are common among chronic dialysis patients even without leukemia.[39] Furthermore, among chronic dialysis patients, asymptomatic carriers of resistant bacteria are prevalent.[40-42]

Table 2. Select precautions and recommendation for AML therapy in patients with renal or hepatic dysfunction

	Specific supportive care considerations	Induction therapy	Postremission strategy
Renal failure[27,29,32]	1. Caution with fluid balance 2. Loop diuretics 3. Avoid sodium bicarbonate 4. Leukapheresis for TLS prevention 5. Adjust allopurinol dose	1. "3+7" with regular cytarabine dose 2. Reduce daunorubicin by 50% if creatinine >3 mg/dL	1. Mitoxantrone + etoposide preferred 2. Dose-adjusted HiDAC not recommended
Dialysis[27]	Use dialysis to balance electrolytes and prevent TLS	"3+7" with reduced anthracycline dose: depending on anticipated prognosis from the renal disease	Repeat induction regimen
Hepatic cirrhosis[65,66]	Careful monitoring for coagulopathy	Dose reduction based on bilirubin blood level If bilirubin >5 mg/dL, maximum cytarabine dose is 50 mg/m^2	

"3+7", 3 days of daunorubicin and 7 days of cytarabine.

A curative approach to AML may be futile among patients in whom the predicted survival due to their kidney disease is short even prior to the development of leukemia.[43,44] Realistic expectations and the desired goals of therapy must be discussed between the patient, family, nephrologist, and hematologist. For a newly diagnosed AML patient who has a favorable prognosis based on the dialysis comorbidity scale,[43,44] AML therapy with curative intent is reasonable.

The induction regimen and chemotherapy doses are similar to those described above for patients with severely impaired renal function. Because anthracyclines are not eliminated by hemodialysis, no dose augmentation is required.[31]

As postremission therapy,[45] high-dose cytarabine should be avoided due to potential neurotoxicity.[46] We would recommend repeating the induction regimen for 1 to 2 cycles or, alternatively, administer mitoxantrone and etoposide in reduced doses. Allogeneic transplantation in patients on chronic dialysis has been reported.[47,48] Ordinarily, we do not consider it except in rare cases of a young highly motivated individual who has a very poor-prognosis genotype.

Comment

Renal dysfunction presents a significant barrier to treatment of AML. Meticulous attention to metabolic abnormalities and chemotherapy dose adjustment are critical.

Scenario 5: patient with hepatitis

A 26-year-old woman presents with core-binding factor AML with the t (8;21)(q22;q22) translocation. Her past medical history is unremarkable. She now resides in the United Kingdom, has traveled extensively as part of a diplomat's family, and was born in China where she spent the first 6 years of her life. In her metabolic profile, the liver and renal function tests are normal. The patient is hepatitis B surface antigen (HBsAg)-positive and antibody to hepatitis B core antigen (anti-HBc)-positive. Antibodies to hepatitis B surface antigen (anti-HBS) are negative.

Questions

Do doses of induction and consolidation need to be attenuated?
Would such a serologic profile preclude an option of allogeneic transplantation?
Is there an optimal antiviral agent and recommended duration for prophylaxis?
Are the guidelines similar if such a patient presents in frank reactivation of hepatitis with markedly abnormal liver enzymes?
What is the best way to monitor response to antiviral therapy?
Should every AML patient, even if they have not lived in high-risk areas, be screened for hepatitis B virus?
What if the patient is a carrier of hepatitis C?

This patient clearly is a carrier of hepatitis B virus and is at significant risk for hepatitis B virus (HBV) reactivation (HBVr). In general, HBsAg and anti-HBc are positive in such patients. Anti-HBc is the most sensitive test for previous exposure to hepatitis B and may be positive in the absence of detectable HBsAg. In rare cases, both the surface antigen and antibodies to the core antigen may be negative, whereupon prior exposure can be detected by sensitive polymerase chain reactions (PCRs) for DNA load. However, this is not part of routine practice in most parts of the world.

Prophylaxis is essential for patients receiving severe immunosuppressive therapy. AML induction and consolidation therapy certainly fall into this category.[49] The efficacy of such prophylaxis has been demonstrated in several controlled trials.[50,51] With prophylaxis, induction and consolidation therapy can be given at standard doses, and if indicated, allogeneic transplantation can be undertaken. The presence of antibody to HBsAg may offer some protection, but this is probably insufficient to discard prophylaxis.[52]

Whether patients who are at low risk for HBVr should be screened is controversial. However, given the high risk of morbidity and mortality (~25%),[53] and in light of the marked efficacy of prophylaxis, we routinely screen all newly diagnosed AML patients for HBsAg and anti-HBc.[54,55]

Lamivudine remains the most commonly used agent as prophylaxis, which should ordinarily be continued for a total of 6 to 12 months. The ideal monitoring of response uses DNA viral load. However, lamivudine is associated with a high rate of developing drug resistance over time (>20% at 1 year). Therefore, in those parts of the world where cost is not the primary determining factor, therapy with next-generation nucleotide analogs should be given to AML patients. Entecavir is an alternative to lamivudine, and is particularly suitable for naive patients with no history of resistance to therapy or prior reactivation.[56] In the latter case, the preferred agent is tenofovir disoproxil fumarate.

In the presence of HBVr, with high HBV DNA levels and frank hepatitis, prompt use of antiviral therapy does not in itself permit the use of standard chemotherapy for AML. Management of such cases is complex, leads to significant delays and, often, discontinuation of therapy. Considerable experience is needed in navigating the risks of progressive hepatic failure with ongoing immunosuppression.[57-59]

In patients with cancer, reactivation of hepatitis C virus (HCV) is far less common and associated with significantly lower rates of severe

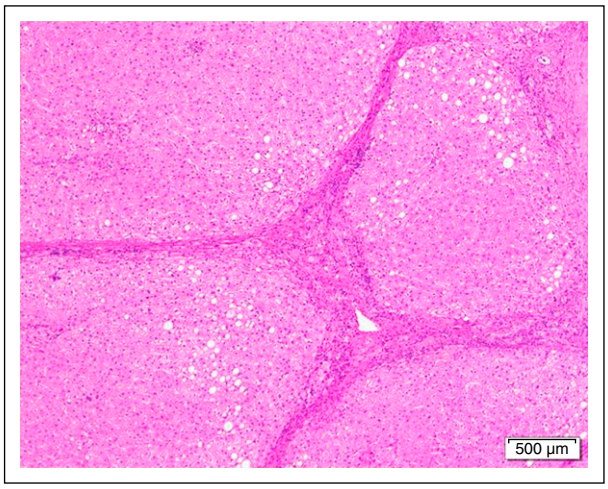

Figure 2. Photomicrograph of a cirrhotic liver illustrating well developed fibrous septa separating irregular regenerative nodules. The hepatocytes show mild steatosis (hematoxylin and eosin stain, original magnification ×40).

hepatitis than HBV reactivation.[60] Current guidelines by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America do not recommend prophylaxis for HCV reactivation, certainly not in asymptomatic carriers or in those with noncirrhotic hepatitis.[61] Among patients with cirrhosis, the risk of life-threatening reactivation is greater.[62]

Nevertheless, this is clearly an area of flux in the era of novel therapies for HCV. There has been a suggestion that patients receiving potent immunosuppressive targeted therapies should be closely monitored for potential development of hepatic flare,[63] but this is controversial in a new era of clinical investigations, and there are no special guidelines for patients with AML.

Comment

Although not proven, AML and its therapy are sufficiently immunosuppressive to recommend prophylaxis for all carriers of hepatitis B. Prophylaxis is not recommended for carriers of hepatitis C.

Scenario 6: patient with cirrhosis

A 58-year-old man with cirrhosis (Figure 2) of the liver attributable to chronic alcohol abuse is found to have AML with the mixed-lineage leukemia translocation t(4;11)(q21;q23). He has evidence of portal hypertension as manifested by mild ascites and edema of the lower extremities. The serum albumin is mildly low at 3.0 g/dL and the prothrombin time and partial thromboplastin time are slightly prolonged.

Questions

Can patients with cirrhosis receive treatment of AML?
What is the preferred regimen?
Are there dose modifications of chemotherapeutic agents?

The treatment of a patient with cirrhosis of the liver and newly diagnosed AML is complicated. Underlying cirrhosis of the liver presents a number of potential issues. These include third spacing of fluid, hepatic dysfunction with perturbed drug metabolism, portal hypertension and variceal bleeding, malnutrition and coagulopathy due to impaired synthetic function as well as thrombocytopenia related to splenic sequestration. As a result, many patients may not be candidates for intensive chemotherapy. The Child-Pugh score is an important tool for determining the prognosis of patients with cirrhosis.[64] Coagulation abnormalities need to be very closely followed, with aggressive replacement for any evidence of bleeding. In general, we would maintain a platelet count $>20 \times 10^9$/L throughout induction. The therapeutic strategy depends on drug metabolism and dose modification in the setting of hepatic dysfunction.

Because anthracyclines are metabolized primarily by the liver, dose modifications based on the total bilirubin and hepatic transaminases are required.[65,66] For example, we give 75% of the dose of daunorubicin if the total bilirubin is 1.5 to 3 mg/dL and/or the aspartate transaminase (AST) is 60 to 180, 50% dose if the total bilirubin is 3.1 to 5 mg/dL and/or the AST is >180; we do not administer daunorubicin at all if the total bilirubin is >5 mg/dL.[65,66] For cytarabine, because the drug is partially detoxified in the liver, we adjust the dose and administer 50% of the total dose for any elevation in the AST or alanine transaminase[67] or total bilirubin >2 mg/dL.[68] Regarding high-dose cytarabine (HiDAC) for consolidation, theoretically the same criteria for dose modification apply. However, given the numerous potential complications in a patient with cirrhosis of the liver and the risk of cerebellar toxicity, we rarely administer HiDAC in this clinical condition.[69,70]

Decitabine is eliminated by cytidine deaminase which is found intracellularly in the liver. Most clinical trials involving decitabine and azacitidine excluded patients with significant liver disease. Azacitidine has the potential for hepatotoxicity in patients with liver disease.[71,72] Therefore, we do not administer hypomethylating agents to patients with significant preexisting hepatic impairment.

In practice, a patient with cirrhosis and a bilirubin level >5 mg/dL is precluded from optimal induction and consolidation therapy. Low-dose cytarabine may be used; however, our practice is to offer a 7- to 10-day course of cytarabine at a dose not exceeding 50 mg/m^2 per day, given that with standard-dose cytarabine 35% of patients can achieve complete remission (CR).

Allogeneic transplantation is obviously hazardous and we would not do it for anyone with uncompensated cirrhosis. However, in a patient with Child I cirrhosis, who is in CR, we would consider RIC transplantation.

The one theoretic exception where underlying cirrhosis may not preclude treatment of AML may be patients with acute promyelocytic leukemia.[73] In fact, in preclinical models, all-trans retinoic acid has been proposed as a treatment of cirrhosis of the liver because this agent decreases liver fibrosis by reducing transforming growth factor β 1, interleukin-6, and type I collagen.[74,75]

Comment

Cirrhosis of the liver presents a serious dilemma; dose reduction is often required and curative options are usually precluded if associated with severe hyperbilirubinemia.

Scenario 7: patient with COPD

A 62-year-old woman, heavy smoker, known to suffer from pulmonary emphysema (Figure 3) and secondary pulmonary hypertension, presents with pancytopenia and 30% blasts on BM examination. At rest, she is comfortable with oxygen saturation of 90% but even ordinary physical activity causes undue dyspnea. In retrospect, her hemoglobin was falling slowly during the last year and severe

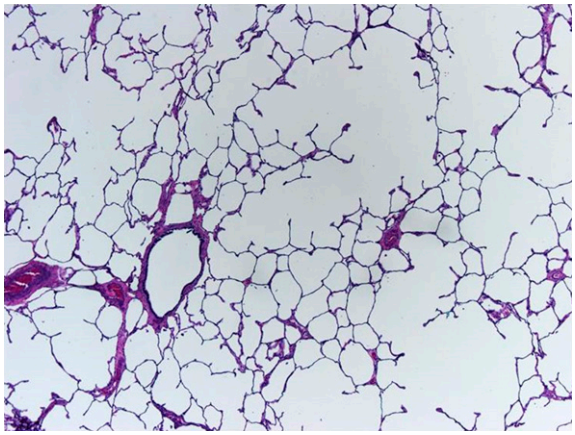

Figure 3. This lung shows centrilobular emphysema with dropout of alveolar walls surrounding the bronchiole (hematoxylin and eosin stain, original magnification ×4).

dysplastic changes are evident in the BM. Unfavorable-risk AML is diagnosed after trisomy 8 and deletion 7 are reported by rapid fluorescence in situ hybridization evaluation.

Questions

What is the best first-line therapy in this woman?
What can be achieved beyond remission?
Are there special recommendations for such patients?

AML patients with chronic obstructive lung disease (COPD) are usually excluded from clinical trials. Therefore, data addressing outcome of such patients are scanty. In a large retrospective study, following intensive induction therapy, grade 3-4 respiratory complications requiring support were present in 16% of AML patients and 8% developed respiratory failure.[76,77] In addition, pulmonary hypertension raises the mortality from sepsis.[78] At the age 62 years, with COPD, patients with AML that evolved from myelodysplastic syndrome need to overcome significant obstacles inherent in intensive chemotherapy.

The Sorror comorbidity index assigns 2 or 3 points for moderate or severe pulmonary abnormalities such as in this patient.[79] A Sorror index of 3 is the cutoff for poorer allogeneic hematopoietic cell transplantation (allo-HCT) outcome even if RIC is carried out[80,81] that similarly applies to intensive induction therapy.[82,83] Given an induction mortality of close to 85% for patients with a Sorror score of 3 or more, the risk of using optimal induction therapy is probably excessive. Hypomethylating therapy may be an alternative to intensive induction as it may be efficacious for "low proliferative" leukemia as well as in frail patients.[84-87] Yet, although hypomethylating agents are better tolerated by patients with comorbidities, the CR rate is only 18% to 24%. A similar 2- to 3-year survival can be expected in patients over 70 years of age following either standard induction or hypomethylating agents.[87] In contrast, in patients 60 to 70 years old, longer survival has been reported if intensive induction is used (25% vs 5% to 8%). For patients with COPD with a slowly proliferating leukemia or with an adverse karyotype, a reasonable strategy is to use hypomethylating therapy for 3 to 4 months followed by RIC allo-HCT.[88-91]

For this patient, we would initiate comprehensive pulmonary function evaluation as results of pulmonary function tests are predictive for long-term outcome of allo-HCT.[92,93] If the patient has a comorbidity score of 3 or greater, and this is consistent with the bedside clinical assessment, we would initiate induction therapy with hypomethylating agents. We would not ordinarily proceed with allogeneic transplantation in this setting. If, on the other hand, the comorbidity score is <3 and the patient is clinically judged as able to tolerate intensive myelosuppression, we would initiate standard induction, recognizing the potential for pulmonary and infectious complications. Intensive support throughout induction is essential as every effort must be made to avoid mechanical ventilation.

As a heavy smoker, this patient is at a particularly high risk for invasive pulmonary infection.[94] Maintaining a high index of suspicion and initiating antifungal prophylaxis are indicated.

Comment

The management of AML patients with COPD is fraught with hazards. In the absence of unequivocal guidelines, the approach to therapy requires experience, careful judgment, and subspecialty support.

Scenario 8: patient with ICH

A 57-year-old woman is diagnosed with acute myelomonocytic leukemia 6 weeks following an intracranial hemorrhage (ICH) involving her right basal ganglia. At the time of the ICH, the blood counts were normal. Her medical history is remarkable only for untreated hypertension. Following successful rehabilitation, she currently can manage her daily life activities but requires walker assistance for mobilization. Currently, her white blood count is 45×10^9/L with 90% blasts. No metaphases are available for analysis, but Flt3-ITD mutation is detected by PCR. The hemoglobin is 11.2 g/dL and the platelet count is 90×10^9/L. Blood coagulation test results are normal. No new neurological abnormalities are present.

Questions

What is the risk of rebleeding in the central nervous system (CNS)? And how does this impact on the therapy for AML?

In a patient with a prior ICH, blood pressure control reduces recurrent CNS bleeding risk by 50%.[95] In addition, urgent antileukemia therapy with the aim to control the blast count is indicated because hyperleukocytosis is associated with increasing bleeding risk.[96-98] A platelet count threshold of 50×10^9/L has been suggested, although there are no convincing data to support this.[99] The risk of rebleeding decreases with time from the primary bleeding event. In this patient, given that she is 6 weeks after the acute event, we would, arbitrarily, maintain the platelet count above 30×10^9/L during standard induction therapy. Such a recommendation may be analogous to guidelines for a similar clinical scenario regarding the use of anticoagulation following ICH.[100] Induction with attenuated anthracycline doses should be avoided as the severity of thrombocytopenia is identical for daunorubicin (45-90 mg/m^2) doses in both younger and older patients with AML.[101,102]

In older patients, in whom the risk of rebleeding is significantly high and allogeneic transplantation is not a practical option, we consider less myeloablative therapy, such as hydroxyurea, low-dose cytarabine, or hypomethylating agents.[100,103]

This patient has a high risk for CNS involvement based on the myelomonocytic lineage morphology and leukocytosis[104-106] but there is no firm evidence to suggest a connection between ICH and CNS involvement of leukemia.[107] Although ICH preceded the diagnosis of leukemia by 6 weeks and the patient has poorly controlled hypertension

as a risk factor for ICH, we would evaluate for the presence of CNS leukemia with a lumbar puncture and imaging.

Comment

Patients with ICH can receive optimal induction therapy, provided the platelets are kept at relatively safe levels.

Conclusion

In conclusion, the presentation of patients with preexisting comorbidities is common and the therapy is challenging. Although certainly not all-encompassing, select common scenarios were presented emphasizing practical approaches for patients who nevertheless require therapy. The catastrophic prognosis for untreated AML often permits and encourages the adoption of pragmatic risk taking. With appropriate subspecialty support, many patients with AML who present with organ dysfunction can be treated successfully.

Acknowledgments

The authors acknowledge the following physicians for their subspecialty advice: Mark Klutstein, Yoav Luria, Arthur Kerner, Daniel Kurnik, Sergio Girlat, William Travis, Richard Steingart, Jinru Shia, and Carlos Flombaum. The authors also thank Hillard Lazarus and Aaron Rapoport for review of the manuscript and helpful suggestions. Finally, the authors thank Sonia Kamenetsky for assistance in the preparation of this manuscript.

Authorship

Contribution: Y.O., M.S.T., and J.M.R. wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Yishai Ofran, Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, 8, Ha'Aliya St, Haifa 31096, Israel; e-mail: y_ofran@rambam.health.gov.il.

References

1. Mengis C, Aebi S, Tobler A, Dähler W, Fey MF. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. *J Clin Oncol.* 2003;21(21):3933-3939.
2. Foley TA, Mankad SV, Anavekar NS, et al. Measuring left ventricular ejection fraction – techniques and potential pitfalls. *Eur Cardiol.* 2012;8(2):108-114.
3. Todaro MC, Oreto L, Qamar R, Paterick TE, Carerj S, Khandheria BK. Cardioncology: state of the heart. *Int J Cardiol.* 2013;168(2):680-687.
4. Barrett-Lee PJ, Dixon JM, Farrell C, et al. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. *Ann Oncol.* 2009;20(5):816-827.
5. Rowe JM, Neuberg D, Friedenberg W, et al; Eastern Cooperative Oncology. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. *Blood.* 2004;103(2):479-485.
6. Brunnberg U, Mohr M, Noppeney R, et al. Induction therapy of AML with ara-C plus daunorubicin versus ara-C plus gemtuzumab ozogamicin: a randomized phase II trial in elderly patients. *Ann Oncol.* 2012;23(4):990-996.
7. Kessler T, Mohr M, Müller-Tidow C, et al. Amsacrine containing induction therapy in elderly AML patients: comparison to standard induction regimens in a matched-pair analysis. *Leuk Res.* 2008;32(3):491-494.
8. Oliveira GH, Al-Kindi SG, Caimi PF, Lazarus HM. Maximizing anthracycline tolerability in hematologic malignancies: Treat to each heart's content. *Blood Rev.* 2016;30(3):169-178.
9. Eschenhagen T, Force T, Ewer MS, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2011;13(1):1-10.
10. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol.* 2009;53(24):2231-2247.
11. Wouters KA, Kremer LC, Miller TL, Herman EH, Lipshultz SE. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. *Br J Haematol.* 2005; 131(5):561-578.
12. Alderton PM, Gross J, Green MD. Comparative study of doxorubicin, mitoxantrone, and epirubicin in combination with ICRF-187 (ADR-529) in a chronic cardiotoxicity animal model. *Cancer Res.* 1992;52(1):194-201.
13. Yamaguchi N, Fujii T, Aoi S, Kozuch PS, Hortobagyi GN, Blum RH. Comparison of cardiac events associated with liposomal doxorubicin, epirubicin and doxorubicin in breast cancer: a Bayesian network meta-analysis. *Eur J Cancer.* 2015;51(16):2314-2320.
14. McMurray JJ, Adamopoulos S, Anker SD, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2012;14(8): 803-869.
15. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer.* 2010;10:337.
16. Sarkiss MG, Yusuf SW, Warneke CL, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. *Cancer.* 2007;109(3):621-627.
17. Yusuf SW, Iliescu C, Bathina JD, Daher IN, Durand JB. Antiplatelet therapy and percutaneous coronary intervention in patients with acute coronary syndrome and thrombocytopenia. *Tex Heart Inst J.* 2010;37(3):336-340.
18. Qaseem A, Humphrey LL, Fitterman N, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2013; 159(11):770-779.
19. Sekeres MA, Elson P, Kalaycio ME, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood.* 2009;113(1):28-36.
20. van Dalen EC, van der Pal HJ, Kremer LC. Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy. *Cochrane Database Syst Rev.* 2016;3:CD005008.
21. Willard JE, Lange RA, Hillis LD. The use of aspirin in ischemic heart disease. *N Engl J Med.* 1992;327(3):175-181.
22. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet.* 1990; 336(8719):827-830.
23. Montesinos P, Lorenzo I, Martín G, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. *Haematologica.* 2008;93(1):67-74.
24. Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: practice management. *Blood Rev.* 2012;26(3):117-122.
25. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol.* 2008;26(16): 2767-2778.
26. Dalbeth N, Stamp L. Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. *Semin Dial.* 2007;20(5):391-395.
27. Fissell WH, Earl M. Pharmacokinetics of anti-cancer chemotherapy in renal insufficiency and dialysis. In: Finkel KW, Howard SC, eds. Renal Disease in Cancer Patients. Amsterdam, The Netherlands: Academic Press Elsevier; 2014: 251-269.
28. Damon LE, Mass R, Linker CA. The association between high-dose cytarabine neurotoxicity and renal insufficiency. *J Clin Oncol.* 1989;7(10): 1563-1568.
29. Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for

altered renal function. *Cancer Treat Rev.* 1995; 21(1):33-64.

30. Appelbaum FR, Kopecky KJ, Tallman MS, et al. The clinical spectrum of adult acute myeloid leukaemia associated with core binding factor translocations. *Br J Haematol.* 2006;135(2): 165-173.
31. Yoshida H, Goto M, Honda A, et al. Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis. *Cancer Chemother Pharmacol.* 1994;33(6):450-454.
32. Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *Eur J Cancer.* 2007;43(1):14-34.
33. Niscola P, Vischini G, Tendas A, et al. Management of hematological malignancies in patients affected by renal failure. *Expert Rev Anticancer Ther.* 2011;11(3):415-432.
34. Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. *Ann Oncol.* 2010;21(7): 1395-1403.
35. Alberts DS, Peng YM, Bowden GT, Dalton WS, Mackel C. Pharmacology of mitoxantrone: mode of action and pharmacokinetics. *Invest New Drugs.* 1985;3(2):101-107.
36. Aronoff GB, ed. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. 5th ed. Washington, DC: American College of Physicians; 2007.
37. Stewart CF. Use of etoposide in patients with organ dysfunction: pharmacokinetic and pharmacodynamic considerations. *Cancer Chemother Pharmacol.* 1994;34(suppl): S76-S83.
38. Jones GL, Will A, Jackson GH, Webb NJ, Rule S; British Committee for Standards in Haematology. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol.* 2015;169(5):661-671.
39. Vogelzang JL, van Stralen KJ, Noordzij M, et al. Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA registry. *Nephrol Dial Transplant.* 2015;30(6):1028-1037.
40. Nguyen DB, Lessa FC, Belflower R, et al; Active Bacterial Core Surveillance (ABCs) MRSA Investigators of the Emerging Infections Program. Invasive methicillin-resistant Staphylococcus aureus infections among patients on chronic dialysis in the United States, 2005-2011. *Clin Infect Dis.* 2013;57(10): 1393-1400.
41. Crowley L, Pitcher D, Wilson J, Guy R, Fluck R. UK Renal Registry 16th annual report: chapter 15 epidemiology of reported infections amongst patients receiving dialysis for established renal Failure in England from May 2011 to April 2012: a joint report from Public Health England and the UK Renal Registry. *Nephron Clin Pract.* 2013; 125(1-4):295-308.
42. Zacharioudakis IM, Zervou FN, Ziakas PD, Rice LB, Mylonakis E. Vancomycin-resistant enterococci colonization among dialysis patients: a meta-analysis of prevalence, risk factors, and significance. *Am J Kidney Dis.* 2015;65(1):88-97.
43. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med.* 2000;108(8):609-613.
44. Cohen LM, Ruthazer R, Moss AH, Germain MJ. Predicting six-month mortality for patients who are on maintenance hemodialysis. *Clin J Am Soc Nephrol.* 2010;5(1):72-79.
45. Rowe JM. Optimal induction and post-remission therapy for AML in first remission. *Hematology Am Soc Hematol Educ Program.* 2009;2009: 396-405.
46. Rubin EH, Andersen JW, Berg DT, Schiffer CA, Mayer RJ, Stone RM. Risk factors for high-dose cytarabine neurotoxicity: an analysis of a cancer and leukemia group B trial in patients with acute myeloid leukemia. *J Clin Oncol.* 1992;10(6): 948-953.
47. Bischoff ME, Blau W, Wagner T, et al. Total body irradiation and cyclophosphamide is a conditioning regimen for unrelated bone marrow transplantation in a patient with chronic myelogenous leukemia and renal failure on hemodialysis. *Bone Marrow Transplant.* 1998;22(6):591-593.
48. Perry JJ, Fleming RA, Rocco MV, et al. Administration and pharmacokinetics of high-dose cyclophosphamide with hemodialysis support for allogeneic bone marrow transplantation in acute leukemia and end-stage renal disease. *Bone Marrow Transplant.* 1999; 23(8):839-842.
49. Ludwig E. HBV reactivation in immunosuppressed patients: prevention or containment? *Hepatology.* 2014;59(6): 2062-2064.
50. Yeo W, Chan PK, Ho WM, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol.* 2004;22(5):927-934.
51. Fukushima N, Mizuta T, Tanaka M, et al. Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. *Ann Oncol.* 2009;20(12):2013-2017.
52. Yeo W, Zee B, Zhong S, et al. Comprehensive analysis of risk factors associating with hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer.* 2004;90(7):1306-1311.
53. Roche B, Samuel D. The difficulties of managing severe hepatitis B virus reactivation. *Liver Int.* 2011;31(suppl 1):104-110.
54. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy [published correction appears in *Gastroenterology.* 2015; 148(2):455]. *Gastroenterology.* 2015;148(1): 215-219.
55. Artz AS, Somerfield MR, Feld JJ, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol.* 2010;28(19):3199-3202.
56. Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol.* 2013;31(22): 2765-2772.
57. Visram A, Feld JJ. Defining and grading HBV reactivation. *Clin Liver Dis.* 2015;5(2):35-38.
58. Kamitsukasa H, Iri M, Tanaka A, et al. Spontaneous reactivation of hepatitis B virus (HBV) infection in patients with resolved or occult HBV infection. *J Med Virol.* 2015;87(4):589-600.
59. Lan JL, Chen YM, Hsieh TY, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis.* 2011;70(10):1719-1725.
60. Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat Rev Clin Oncol.* 2012;9(3):156-166.
61. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. Available at http://hcvguidelines.org/. Accessed March 2016.
62. Coppola N, Pisaturo M, Guastafierro S, et al. Increased hepatitis C viral load and reactivation of liver disease in HCV RNA-positive patients with onco-haematological disease undergoing chemotherapy. *Dig Liver Dis.* 2012;44(1):49-54.
63. Yazici O, Sendur MA, Aksoy S. Hepatitis C virus reactivation in cancer patients in the era of targeted therapies. *World J Gastroenterol.* 2014; 20(22):6716-6724.
64. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg.* 1973;60(8):646-649.
65. Perry MC, ed. The Chemotherapy Source Book. 2nd ed. Baltimore, MD: Williams and Wilkins; 1996.
66. Haddadin S, Perry MC. Chemotherapeutic agents: idarubicin. In: Perry MC, ed. The Chemotherapy Source Book. 5th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2012:659-739.
67. Floyd J, Mirza I, Sachs B, Perry MC. Hepatotoxicity of chemotherapy. *Semin Oncol.* 2006;33(1):50-67.
68. Koren G, Beatty K, Seto A, Einarson TR, Lishner M. The effects of impaired liver function on the elimination of antineoplastic agents. *Ann Pharmacother.* 1992;26(3):363-371.
69. Donehower RC, Karp JE, Burke PJ. Pharmacology and toxicity of high-dose cytarabine by 72-hour continuous infusion. *Cancer Treat Rep.* 1986;70(9):1059-1065.
70. King PD, Perry MC. Hepatotoxicity of chemotherapy. *Oncologist.* 2001;6(2):162-176.
71. Bellet RE, Mastrangelo MJ, Engstrom PF, Custer RP. Hepatotoxicity of 5-azacytidine (NSC-102816) (a clinical and pathologic study). *Neoplasma.* 1973;20(3):303-309.
72. Weiss AJ, Metter GE, Nealon TF, et al. Phase II study of 5-azacytidine in solid tumors. *Cancer Treat Rep.* 1977;61(1):55-58.
73. Yamane A, Tsukamoto N, Saitoh T, et al. Successful treatment by all-trans retinoic acid in a patient with acute promyelocytic leukemia complicated by liver cirrhosis and polycystic kidney. *Intern Med.* 2009;48(18):1691-1694.
74. Hisamori S, Tabata C, Kadokawa Y, et al. All-trans-retinoic acid ameliorates carbon tetrachloride-induced liver fibrosis in mice through modulating cytokine production. *Liver Int.* 2008;28(9):1217-1225.
75. Wang L, Potter JJ, Rennie-Tankersley L, Novitskiy G, Sipes J, Mezey E. Effects of retinoic acid on the development of liver fibrosis produced by carbon tetrachloride in mice. *Biochim Biophys Acta.* 2007;1772(1):66-71.
76. Atallah E, Cortes J, O'Brien S, et al. Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia. *Blood.* 2007;110(10): 3547-3551.
77. Al Ameri A, Koller C, Kantarjian H, et al. Acute pulmonary failure during remission induction chemotherapy in adults with acute myeloid leukemia or high-risk myelodysplastic syndrome. *Cancer.* 2010;116(1):93-97.

78. Tsapenko MV, Herasevich V, Mour GK, et al. Severe sepsis and septic shock in patients with pre-existing non-cardiac pulmonary hypertension: contemporary management and outcomes. *Crit Care Resusc.* 2013;15(2): 103-109.

79. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106(8):2912-2919.

80. Sorror M, Storer B, Sandmaier BM, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. *Cancer.* 2008;112(9): 1992-2001.

81. Yamamoto W, Ogusa E, Matsumoto K, Maruta A, Ishigatsubo Y, Kanamori H. Predictive value of risk assessment scores in patients with hematologic malignancies undergoing reduced-intensity conditioning allogeneic stem cell transplantation. *Am J Hematol.* 2014;89(9): E138-E141.

82. Giles FJ, Borthakur G, Ravandi F, et al. 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. *Br J Haematol.* 2007;136(4):624-627.

83. Savic A, Kvrgic V, Rajic N, et al. The hematopoietic cell transplantation comorbidity index is a predictor of early death and survival in adult acute myeloid leukemia patients. *Leuk Res.* 2012;36(4):479-482.

84. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J Clin Oncol.* 2010; 28(4):556-561.

85. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol.* 2010;28(4): 562-569.

86. Lübbert M, Rüter BH, Claus R, et al. A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy. *Haematologica.* 2012;97(3): 393-401.

87. Quintás-Cardama A, Ravandi F, Liu-Dumlao T, et al. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. *Blood.* 2012; 120(24):4840-4845.

88. Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pretransplantation therapy with azacitidine vs induction chemotherapy and posttransplantation outcome in patients with MDS. *Biol Blood Marrow Transplant.* 2012;18(8):1211-1218.

89. Bally C, Thépot S, Quesnel B, et al. Azacitidine in the treatment of therapy related myelodysplastic syndrome and acute myeloid leukemia (tMDS/AML): a report on 54 patients by the Groupe Francophone Des Myelodysplasies (GFM). *Leuk Res.* 2013;37(6):637-640.

90. Garelius H, Grund S, Stockelberg D. Induction with azacytidine followed by allogeneic hematopoietic stem cell transplantation in a Jehovah's Witness with acute monocytic leukemia. *Clin Case Rep.* 2015;3(5):287-290.

91. Ahn JS, Kim YK, Min YH, et al. Azacitidine pre-treatment followed by reduced-intensity stem cell transplantation in patients with higher-risk myelodysplastic syndrome. *Acta Haematol.* 2015;134(1):40-48.

92. Walter EC, Orozco-Levi M, Ramirez-Sarmiento A, et al. Lung function and long-term complications after allogeneic hematopoietic cell transplant. *Biol Blood Marrow Transplant.* 2010;16(1):53-61.

93. Piñana JL, Martino R, Barba P, et al. Pulmonary function testing prior to reduced intensity conditioning allogeneic stem cell transplantation in an unselected patient cohort predicts posttransplantation pulmonary complications and outcome. *Am J Hematol.* 2012;87(1):9-14.

94. Caira M, Candoni A, Verga L, et al; SEIFEM Group (Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne). Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1,192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010-a multicenter study). *Haematologica.* 2015;100(2):284-292.

95. Chapman N, Huxley R, Anderson C, et al; Writing Committee for the PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke.* 2004;35(1):116-121.

96. Nowacki P, Zdziarska B, Fryze C, Urasiński I. Co-existence of thrombocytopenia and hyperleukocytosis ('critical period') as a risk factor of haemorrhage into the central nervous system in patients with acute leukaemias. *Haematologia (Budap).* 2002;31(4):347-355.

97. Kim H, Lee JH, Choi SJ, Kim WK, Lee JS, Lee KH. Analysis of fatal intracranial hemorrhage in 792 acute leukemia patients. *Haematologica.* 2004;89(5):622-624.

98. Chen CY, Tai CH, Tsay W, Chen PY, Tien HF. Prediction of fatal intracranial hemorrhage in patients with acute myeloid leukemia. *Ann Oncol.* 2009;20(6):1100-1104.

99. Zuckerman T, Ganzel C, Tallman MS, Rowe JM. How I treat hematologic emergencies in adults with acute leukemia. *Blood.* 2012;120(10): 1993-2002.

100. Broderick J, Connolly S, Feldmann E, et al; American Heart Association/American Stroke Association Stroke Council; American Heart Association/American Stroke Association High Blood Pressure Research Council; Quality of Care and Outcomes in Research Interdisciplinary Working Group. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Circulation.* 2007;116(16):e391-e413.

101. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med.* 2009;361(13): 1249-1259.

102. Löwenberg B, Ossenkoppele GJ, van Putten W, et al; Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON); German AML Study Group (AMLSG); Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. High-dose daunorubicin in older patients with acute myeloid leukemia [published correction appears in *N Engl J Med.* 2010;362(12):1155]. *N Engl J Med.* 2009;361(13):1235-1248.

103. Dayyani F, Mougalian SS, Naqvi K, et al. Prediction model for mortality after intracranial hemorrhage in patients with leukemia. *Am J Hematol.* 2011;86(7):546-549.

104. Cassileth PA, Sylvester LS, Bennett JM, Begg CB. High peripheral blast count in adult acute myelogenous leukemia is a primary risk factor for CNS leukemia. *J Clin Oncol.* 1988;6(3): 495-498.

105. Rozovski U, Ohanian M, Ravandi F, et al. Incidence of and risk factors for involvement of the central nervous system in acute myeloid leukemia. *Leuk Lymphoma.* 2015;56(5): 1392-1397.

106. Cheng CL, Li CC, Hou HA, et al. Risk factors and clinical outcomes of acute myeloid leukaemia with central nervous system involvement in adults. *BMC Cancer.* 2015;15:344.

107. Jourdan E, Dombret H, Glaisner S, Micléa JM, Castaigne S, Degos L. Unexpected high incidence of intracranial subdural haematoma during intensive chemotherapy for acute myeloid leukaemia with a monoblastic component. *Br J Haematol.* 1995;89(3):527-530.