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Special Article

Performance Status in Elderly Patients With Acute Myeloid Leukemia: Exploring Gene Expression Signatures of Cytokines and Chemokines

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Abstract

Acute myeloid leukemia (AML) is an aggressive disease that predominantly affects elderly patients. Cytokines and chemokines are major players in the pathogenesis of AML. They regulate the disease course and play a deleterious role in the progression of AML. The geriatric population is particularly vulnerable to these mediators as these cytokines and chemokines are also implicated in the development of frailty, fatigue, and declining cognitive function. It is the combination of these adverse effects of cytokines and chemokines that affect performance status and, in turn, the poor prognosis in this age group. Cytokines and chemokines are emerging as therapeutic targets in AML. Future endeavors to treat AML will likely involve cytokines and chemokines as attempts are made to disrupt the bone marrow environment. By modulating the bone marrow stroma, the goal is to create an environment less favorable to AML cells and more favorable to the effects of chemotherapy against AML.

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Background

Acute myeloid leukemia (AML) is the most common acute leukemia in the Western world, with a median age of 68 years at diagnosis (1). AML is a heterogeneous disease, with many disease and host-related factors that determine whether a complete remission (CR) can be achieved and/or sustained with induction chemotherapy. The typical response rates for patients are between 55% and 85%, but in older patients (>60 years of age) these CR rates are much lower, in the 25%–50% range (2). The factors involved in poor response and prognosis include high incidence of poor-prognosis karyotypes (5q–, 7q–), high frequency of preceding myelodysplastic syndromes, and an increased expression of proteins (eg, MDR1) involved in intrinsic resistance to chemotherapeutic agents (2–4). This is compounded by host-related factors, such as poor performance status (PS), comorbidities, and organ function impairment that are a part of the normal aging process.

Cytokines and chemokines play a role in the pathogenesis of AML and can affect the disease and host alike. The bone marrow (BM) microenvironment is a dynamic network of growth factors, cytokines, chemokines, and stromal cells that can promote leukemogenesis and progression of AML (5). Both BM stroma and leukemic blasts promote angiogenesis, which is increased in AML patients (5). In addition, elderly AML patients have been shown in one study to have upregulation of pathways involved in angiogenesis (6). Further,

as we age, we develop cellular senescence—cells permanently withdrawn from the cell cycle (7,8). Senescent cells acquire phenotypic changes, termed the senescence-associated secretory phenotype, that play a role in increased cytokine production and, therefore, tumor production (7).

Tumor cells produce cytokines, but the immune system of the host also produces cytokines in response to the malignancy. Cytokines can be grouped into families including tumor necrosis factors (TNFs), interleukins (ILs), and chemokines. Chemokines are usually grouped into two classes: CCL and CXCL that interact with CCR and CXCR receptors, respectively (9). Chemokines belong to a family of soluble proteins, or cytokines, which regulate cell trafficking, proliferation, and apoptosis. These cells play a role in normal hematopoiesis and angiogenesis as well. Dysregulation of many cytokines including IL-1β, IL-2, IL-4, IL-5, IL-6, TNF-α, IL-8, IL-10, IL-11, IL-12, IL-17, IL-18, IL-11, IL-22, IL-23, TGF-β, and IFN-γ has been implicated in all stages of tumor development from initiation and promotion to invasion and metastasis (10–13). Growth factors like vascular endothelial growth factor, basic fibroblast growth factor, and angiopoietins are the main proangiogenic mediators in acute leukemia (5,14). Certain CXC receptors are more highly expressed in CD34+ AML cells compared with CD34– cells which may help explain the poor prognosis in CD34+ AML (9).

In addition, several geriatrics studies have demonstrated that increased levels of certain cytokines (eg, IL-6, IL-1, IL-2, TNF-α, and CRP) are associated with decreased functional status and may predict for frailty in elderly patients (15–17). IL-6, one of the first cytokines identified with the aging process, is called the "geriatric cytokine" and like the other cytokines can be proinflammatory and sarcopenia inducing, thus leading to decreased functional status and increased mortality (15–17). Some of these "markers of frailty" have previously been demonstrated in elderly colon cancer patients to predict for poor PS and quality of life (QOL) and also have been associated with cancer cachexia and fatigue (16,18).

This review attempts to provide the reader with a better understanding of the role of cytokines and chemokines in the pathogenesis of AML, their effect on the elderly AML host, and finally, how they may be manipulated to aid in the treatment of AML.

Effect of Cytokines and Chemokines on AML (BM Microenvironment)

AML is a highly variable disease, often with an aggressive clinical course. The milieu in which AML cells reside likely contributes the necessary cytokines that drive disease progression (19). AML cells evade physiological growth restrictions and proliferate unabated in concert with various cytokines (19). Interleukins (IL-1, IL-2, IL-3, IL-6, and IL-10), TNF-α, and CCL3 (MIP1-alpha) have all been identified as role players in the symphony of leukemic growth (10–13). Although the effect of cytokines on AML differentiation has been studied, data on whether the cytokine effects are age dependent is lacking.

Interleukins

IL-1 is produced by AML blasts, and increased IL-1 can be detected in the serum. IL-1 has also been shown in vivo and in vitro to stimulate the BM microenvironment, causing leukemic blasts to proliferate. AML blast cells produce IL-6, TNF-α, and IL-I that contribute to the autocrine and paracrine growth of leukemic cells (20). Leukemic blast cells have been implicated as a source of cytokine production, and it is postulated that they initiate and even perpetuate paracrine or autocrine loops (14,21,22). Overexpression of IL-1 receptor accessory protein has been associated with poor overall survival in AML patients (23). Further, interleukin-1 receptor antagonist (IL-1ra), which helps regulate or inhibit IL-1, is significantly less in AML patients than that in normal individuals. AML marrow cells also contain more IL-1β protein than normal control cells, which bestow apoptosis resistance and autostimulation to blast cells (19,23). This imbalanced IL-1 β/IL-1ra cytokine loop in AML results in greater direct IL-1β stimulation and reduced IL-1ra suppressive effects compared with normal marrow (19). Likewise, IL-6 produced by AML stimulates and proliferates AML blasts through the IL-6/IL-6R signaling system. The SDF-1/CXCR4 axis is another such loop and is currently being exploited in trials of CXCR4 antagonist therapy to treat AML.

Stem Cell Factor

This cytokine plays an important role in hematopoiesis through its effects on c-kit. In AML, stem cell factor (SCF) results in proliferation of AML blasts. More than 70% of patients with AML have blast cells that express c-kit (24). Peripheral blood and marrow serum (from aspirated BM; fragmented, homogenized, and centrifuged) of AML patients contains more SCF protein than normal serum (19). These data further suggest that unbalanced cytokine production may make a significant contribution to the abnormal behavior of AML cells.

Tumor Necrosis Factor

Blast cells in AML produce TNF-α which in turn induces endothelial cells to produce macrophages and colony-stimulating factors to further support leukemic growth. It has been postulated that the BM microenvironment aids in the unregulated secretion of TNF-α and IL-1 by AML blasts. A study has shown that, in fact AML blast cells produce biologically active IL-6, TNF-α, and IL-1 (20). This AML-derived TNF-α has the capacity to induce granulocyte/macrophage and granulocyte-CSF production by endothelial cells and to support leukemic growth via a paracrine pathway. Higher TNF-α levels correlate with poorer PS; higher leukocyte counts; higher levels of β2-microglobulin, creatinine, uric acid, and alkaline phosphatase; and lower albumin (25).

Chemokines

Several CCL and CXCL chemokines are involved in regulation of angiogenesis, local T-cell recruitment, regulation of antileukemic T-cell activity, and cellular growth regulation in AML (5). There are homeostatic (or constitutive) cytokines that bind to single chemokine receptors and inflammatory (or inducible) cytokines that bind to several receptors, and each of these receptors can bind several chemokines. No single chemokine has been shown to have any correlation with clinical or biological characteristics in AML, and further, exogenous chemokines usually have no effect on AML blast proliferation without the presence of hematopoietic growth factors (G-CSF, IL-3, SCF, and FLT3-L) (9). Differences in chemokine responsiveness, as well as chemokine release, affect AML cell proliferation and the response difference between patients (9). For example, CXCR4 receptor levels are heterogeneous in AML, and CXCR4 expression in AML has been found to predict disease relapse and even survival (26). Also, studies have demonstrated a correlation between CXCR4 expression on AML cells with FLT3 mutational status and poor outcome (26,27).

Cytokines and chemokines affect the disease course and progression of AML (9). This is true even in other myeloid disorders. For example, myelofibrosis patients with elevated IL-2 and IL-6 levels are more likely to progress to AML (13). Studies after BM transplant (in patients with AML, ALL, CML, NHL, and Ewing's sarcoma) showed

a significant association between high IL-10 serum levels and fatal outcomes (28). High TNF-α levels purport an adverse prognosis, and conversely, TNF-α levels <10 pg/mL are significantly associated with higher rates of CR, survival, and event-free survival (25).

Effect of Cytokines and Chemokines on the Host With AML

Cytokines and chemokines affect PS in AML patients, especially in elderly patients through their impacts on frailty, fatigue, and cognitive function. Increased levels of certain cytokines (IL-6, IL-1, IL-2, TNF-α, and CRP) are associated with decreased functional and PS (17). Figure 1 demonstrates the interactions between the host, tumor, cytokines, and the therapy for tumor.

Performance Status

Traditionally in oncology, PS is used as an attempt to quantify cancer patients' general well-being and is also utilized to determine whether they can receive chemotherapy. PS assessment has become a powerful prognostic tool as well, which helps to guide decision making about treatment (29). The most commonly used measure, ECOG PS, runs from 0 to 5, with 0 denoting perfect health and 5 denoting death (30). A landmark retrospective analysis of 968 AML patients has revealed a strong correlation between age and ECOG PS. In patients aged more than 75 years with a PS of 3, the 30-day mortality from induction therapy was 82% (2). However, in the geriatric oncology population, the ECOG PS might not be sufficient to assess functional status. It has been demonstrated that Comprehensive Geriatric Assessment (CGA) adds substantial information to the functional assessment of elderly cancer patients, including patients with a good ECOG PS (31). Recently, Klepin and colleagues (32) have demonstrated that AML patients with less impairment in CGA measures are more likely to have better ECOG scores.

In addition, one study utilized clinically annotated microarray data (from mRNA expression from BM leukemic blasts) from two data sets with 377 AML patients: GSE1159 and GSE12417 (6). A "frailty profile" was developed by utilizing a set of previously characterized gene sets/pathways that define the following cytokines: IL-6, IL-1, IL-2, TNF-α, and CRP. The frailty profile was then queried in the 377 AML patients and by unsupervised clustering methods, two cohorts (n = 58) of patient samples that represented extremes of survival (cohort 1, median survival [MS] 4.9 months; cohort 2, MS 46.3 months; $p < .0001$) were identified. Standard Kaplan-Meier survival curves were also generated for these 58 patients based on just clinical ECOG PS, and there was no statistically significant difference in overall survival (MS for ECOG 0–1 was 14 months, ECOG ≥ 2 was 8.8 months; p = .29). The authors further stratified these patients into three risk groups: low-, intermediate-, and high-risk depending on (a) cohort based on frailty profile and (b) ECOG PS, to evaluate if the frailty profile adds any additional information to the clinically estimated ECOG PS. This combined analysis revealed that low-risk patients (cohort 2 plus ECOG 0–1) had a statistically significant higher MS of 56.1 months compared with intermediate-risk (MS 9.85 months) and high-risk (MS 8.35 months) patients; p = .02 (6). This suggests that cytokines do indeed add information to an arbitrary clinical parameter like the ECOG PS.

Frailty

Frailty can be defined as a clinical syndrome composed of combinations of unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity (33). Frailty can further be considered in relation to deficit accumulation (34). The "frail elderly" patients have also been

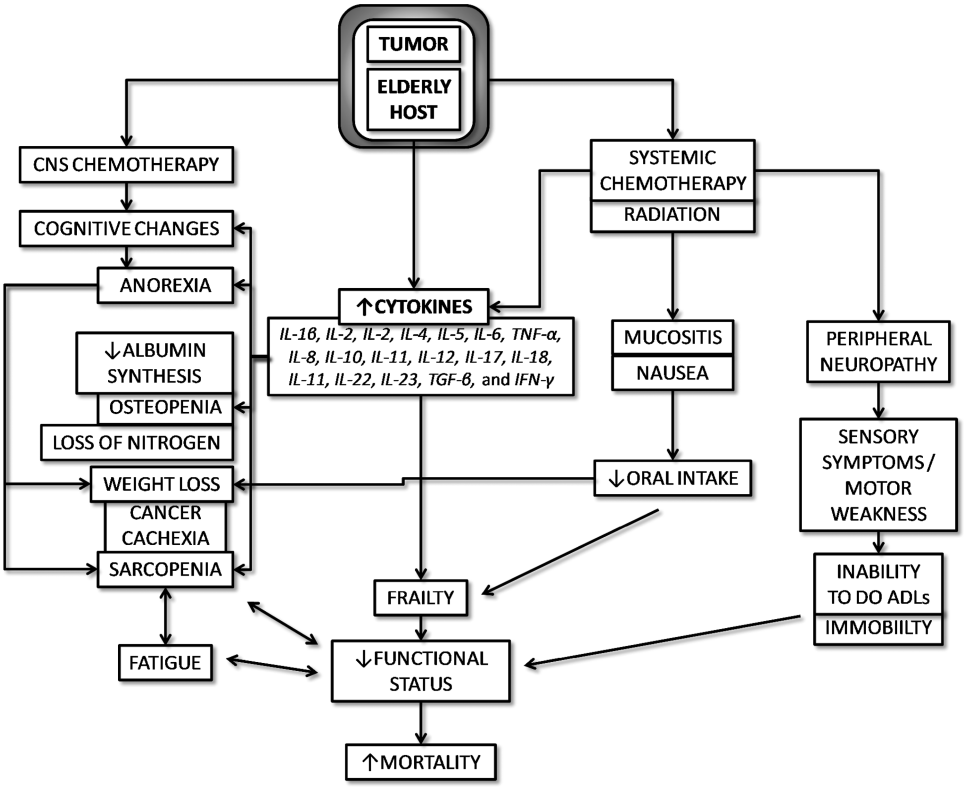

Figure 1. Interaction between host, tumor, cytokines, and therapy for cancer.

defined as those aged more than 65 years with multiple disease processes that functionally limit normal activity (35). This is the group that presents the most challenging problems to the physician and health care professional (35,36). Functional impairment and activity of daily living (ADL) performance are worse in elderly cancer patients than in age-matched controls (36,37). Frailty becomes pertinent in AML patients, because it aids in the discussion of therapy and the aggressiveness of care. Frail patients are less likely to be offered aggressive treatments and more likely to go onto therapy with a hypomethylating agent or even best supportive care. Older patients are not only more likely to have pre-existing frailty but also more apt to become frail and dependent as cancer and its treatments take effect.

There are a number of reasons why elderly patients with AML are more prone to frailty and decreased functional status. Chemotherapy for AML is much more intense than what patients with solid tumors receive and leads to neutropenia and increased infection risk. Prolonged hospitalization and severe anemia contribute to fatigue and immobility. Chemotherapy-related mucositis and colitis affect oral intake and nutrition. Cardiotoxicity and neurotoxicity induced by chemotherapy further make the patients disabled and affect their PS.

Cytokines are largely implicated in the pathophysiology of functional decline and even death in older persons (38). IL-6, the "geriatric cytokine" has been associated with decreased muscle mass and strength, physical performance, balance, and walking speed in elderly patients (15–17). The sarcopenia, anorexia, and cachexia associated with aging are largely due to cytokines, in particular IL-6, IL-1β, TNF-α, and IL-2 (16,18). CXCL-10 is a proinflammatory chemokine studied to have increasing levels with aging. CXCL-10 is upregulated in frail older adults and correlates with higher IL-6 levels in frail adults (39). Functional decline in the geriatric oncology population may partly be dictated by cytokines and chemokines, and the ability to not only associate these molecular makers with disease state but also to utilize them for targeted therapy.

Certain cytokines are increased in AML and in elderly patients and may contribute to frailty, but we cannot conclude that cytokines and chemokines produced in large quantities in acute AML affect frailty. There has not been a large-scale study to show a uniform increase of cytokines in AML patients and not all AML patients will have increases in the same specific cytokines. Some may just have increased IL-6 that contributes to blast proliferation and frailty, whereas others may have a different cytokine profile. Also, it is unknown if elderly patients who exercise, use antioxidants, and so on have lower cytokine levels and are thus less prone to frailty when they develop a disease state like AML. In general, older AML patients likely are more vulnerable; they may have multiple comorbidities, have a more aggressive disease process, and perhaps worse PS. This may, in part, be secondary to increased cytokines and chemokines, but therapeutic factors (chemotherapy, mucositis, and immobilization) also play an important role in sarcopenia, malnutrition, cognitive changes, and falls all leading to a phenotype of a frail individual.

QOL and Fatigue

QOL and fatigue are significantly affected by AML, especially in older adults (40,41). Fatigue, the most prevalent symptom in older cancer patients, is almost universally present in older adults with AML and is associated with reductions in QOL, ADLs, and instrumental ADLs (41). Not just the cancer itself, but chemotherapy as well, has effects on fatigue and QOL, with relatively stable to improved QOL seen in those who survive intensive chemotherapy (42). Furthermore, cytokines are involved in modulating QOL and fatigue, these include IFN-γ, IL-5, IL-8, IL-10, and TNF-α (43). PS, QOL, and fatigue are negatively affected by circulating TNF-α and IL-6 (44).

One study of AML/MDS patients revealed impaired attention span, psychomotor function, motor coordination, and executive function even prior to treatment, with worsening after cytotoxic chemotherapy (45). In this study, higher IL-6, IL-1RA, and TNF-α levels correlated with higher fatigue and poor executive function (45). Although not significant, patients with lower circulating IL-1 levels at baseline were more likely to achieve a complete response (45).

Cognitive Function

The likelihood of having cognitive dysfunction, as well as AML, increases with age. Fatigue, depression, and impaired memory are common in cancer patients, both before and after chemotherapy (45,47). Cognitive impairment is observed in AML and has been linked to higher cytokine levels (45). One specific cytokine, INF-α, has been implicated as the causal agent in a syndrome of mood disturbance, memory impairment, cognitive slowing, and impaired executive function by increasing levels of IL-1, IL-6, and TNF-α (48). An elevated IL-1 level affects memory and causes cognitive impairment (45,49). IL-6 has been linked to Alzheimer's disease pathogenesis and increased levels of IL-2 production correlate with dementia severity (50). IL-2 and INF-α have been reported to induce fatigue, depression, confusion, and decrease mental performance (51). Interestingly, there was a positive correlation between IL-8 levels and memory, with note that IL-8 has previously been reported to enhance brain cell survival (45,46).

Role of Cytokines and Chemokines in the Therapy of AML

There is emerging evidence that cytokines may play a role in the treatment of malignancies and, in particular, in AML. A number of AML cells in the BM survive after cytotoxic chemotherapy, and these cells constitute the minimal residual disease (MRD). The reasons these MRD cells evade the cytotoxicity of chemotherapy are thought to be due to complex interactions between these cells and the BM microenvironment, mainly cytokines and chemokines (52). There have been several small studies evaluating the efficacy of interleukins or antibodies to interleukins in AML patients. Table 1 summarizes a few of the prominent studies that have been conducted.

Cytokines

IL-2 has been studied as an adjuvant to AML treatment and is mainly studied as a remission maintenance therapy for patients in CR. IL-2 recruits T cells and natural killer cells to theoretically enhance cytotoxicity against tumor cells (53,54). Unfortunately, the studies using IL-2 against AML have not shown benefit, and the role of IL-2 moving forward is unclear (54,55). Use of IL-2 in combination with IL-12 may potentiate the antileukemic effects and help diminish some of the adverse side effects of both (56). IL-27, an immunoregulatory cytokine, is part of the IL-12 superfamily and directly induces differentiation in hematopoietic stem cells (HSCs), thus making it potentially useful (57). To date, there are no clinical trials utilizing IL-27 in human AML therapy. IL-3 receptor abnormalities are plentiful in AML cells, and for this reason, antibodies that block IL-3 receptor may represent a new strategy to help eradicate AML cells from the BM (58). Although studies have not shown a survival benefit, there is promise for IL-11 in AML therapies with regard to chemotherapy response rates and decreased bacteremia (54,59,60).

Table 1. Selected Clinical Studies of Cytokines and Chemokines in AML

Therapy	Model	*N*	Treatment Protocol	Response Rate	Side Effects	Future Directions
Cytokines						
IL-2 (55)	Human	905	Meta-analysis of IL-2, monotherapy maintenance for patients in CR	No benefit on OS and LFS of IL-2 over no treatment	Thrombocytopenia and neutropenia	Activity of IL-2 on T cells and natural killer cells needs to be protected from reactive oxygen species
IL-3 (68)	Human	20	Open label Ph1/2 study of IL-3 continuous infusion from 24 h before chemotherapy until day 28	CR 51% (45% in elderly patients)	Rash, headache, fluid retention, bone pain, fevers, and nausea	Further phase 2 and 3 trials are needed
IL-11 (59)	Human	51	Randomized controlled trials of GO ± IL-11	CR: 8% in GO without IL-11 and 36% for GO ± IL-11	Hepatic veno-occlusive disease	Response of GO ± IL-11 is good but no better than historical controls
IL-12 (69)	Human leukemic cell lines		U937, THP-1, and K562 leukemic cell lines cultured ± IL-12	IL-12 impaired significantly ($p <$ .001) the angiogenic activity of all AML cell lines, while not affecting survival and proliferation	NA	Human clinical trials pending
IL-27 (70)	Human leukemic cell lines		AML cell ± IL-27 was studied by chorioallantoic membrane assay and polymerase chain reaction array	IL-27 reduced in vitro AML cell proliferation and modulated the expression of different genes involved in the angiogenic process	NA	Human clinical trials pending
VEGF (14)	In vitro human cells		In vitro study of VEGFR antibodies	VEGFR antibodies inhibited VEGF-stimulated migration of leukemia cells	NA	In mouse model: Anti-VEGF therapies significantly increased duration of survival
Chemokines						
Anti-CXCR4 antibodies (AMD3100/plerixafor) (71)	Human leukemic cell lines		AML cells incubated with CXCR4 or SDF-1-blocking agents, then treated for 3–4 d with AMD3100	SDF-1 promoted AML cell survival. AMD3100 significantly decreased AML survival	ND	CXCR4 has potential as a therapy to inhibit AML stem cell proliferation and migration yet only minimally affects normal SCs
Anti-CXCR4 antibodies (AMD3100/plerixafor) (72)	Human	52	Phase 1/2 study of AMD3100 + mitoxantrone, etoposide, and cytarabine chemotherapy	CR + CRi rate of 46%	Grade 3–4 fever (98%) and grade 3–5 infections (19%)	In addition to CXCR4, molecules like α integrins (VLA-4), selectins (L-selectin), and cell-surface glycoproteins (CD44) may provide alternative targets for simultaneous disruption of multiple adhesion pathways

Note. AML = acute myeloid leukemia; CR = complete remission; GO = Gemtuzumab; IL = interleukin; LFS = leukemia-free survival; SDF-1 = stromal cell–derived factor-1; SC = stem cell; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

Chemokines

One specific chemokine, CXCR4, is the receptor for stromal cell–derived factor-1 (SDF-1). SDF-1 is one of the BM stromal cells linked to AML resistance, and the interaction between the CXCR4 and SDF-1 is essential for leukemic cell motility, proliferation, and survival (61,62). Normal stem cells and AML blasts express CXCR4, and it has been shown to be a negative prognostic indicator for disease relapse and survival (26). CXCR4 antagonists help to mobilize AML cells (especially the MDR cells) from their stromal microenvironments and make them more susceptible to chemotherapy (26). AMD3100 (Plerixafor [Mozobil]) is a CXCR4 antagonist that has been shown to promote AML cell differentiation and to decrease their survival (61).

Studies support the addition of AMD3100 to cytotoxic chemotherapy in AML patients, with encouraging rates of remission, and are FDA approved for use in combination with G-CSF to mobilize HSCs for collection and subsequent autologous transplantation in patients with non-Hodgkin lymphoma and multiple myeloma (61). Data suggest that mobilization and procurement of a functional hematopoietic allograft are more rapid with Plerixafor than the standard, G-CSF (63).

Future Directions

The role that the BM microenvironment plays in drug resistance has become an emerging target for future therapies in AML. There are promising reports of Plerixafor overcoming the chemoresistance mediated by the adhesion of leukemia blasts to marrow stromal cells (64).

There has been investigation into the use of G-CSF prior to chemotherapy in AML to "prime" the marrow and make AML cells more sensitive to chemotherapy (65,66). Similar to G-CSF, Plerixafor effectively mobilizes AML cells, but unlike G-CSF, it does so without inducing their proliferation (66). Trials are underway to explore the combination of G-CSF and Plerixafor in patients with refractory AML. There is further study needed to understand the optimal timing of administration for Plerixafor in order to fully exploit the synergistic effects of chemotherapy and chemokine receptor blockade.

In addition, AML blasts interact with adhesion molecules other than CXCR4. These others include CD117, VLA-4, L-selectin, and CD44, which make up more of the BM microenvironment and are antiapoptotic and antiproliferative as well and have been implicated in chemotherapy resistance (66). For instance, increased binding of soluble vascular cell adhesion molecule-1 has been associated with improved survival in patients with AML, but not surface expression of VLA-4. These molecules are potential targets to disrupt the BM stroma, and even perturb the adhesion of MRD cells, to help modulate the effect of chemotherapy (67).

Induction chemotherapy for AML is a difficult undertaking in the elderly patient with significant loss of functional status leading to institutionalization and increased mortality. Cytokines and chemokines play a huge role in the pathogenesis of AML and can negatively affect an elderly patient's QOL. There continues to be a dearth of studies evaluating the effect of cytokine manipulation with either cytokine directed antibodies or other modalities such as exercise in elderly AML patients. Although CR and overall survival are important outcomes in elderly AML clinical trials, there also needs to be an impetus on including QOL and frailty measures via comprehensive geriatric assessment. It would also be of use to understand and evaluate correlations between these QOL endpoints and serum and BM cytokine levels in elderly AML patients. The ultimate goal of therapy in this patient population should be to maximize response to induction therapy but minimize toxicity from the therapy. A better understanding of the underlying biology with regards to cytokines and chemokines may provide us with a tool to treat these patients more effectively and avoid frailty, functional decline, and morbidity from therapy.

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