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Adult Acute Myeloid Leukemia Long-Term Survivors

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Abstract

The number of Leukemia patients and survivors is growing. This review summarizes what is known regarding the Health Related Quality Of Life (HRQOL) and medical complications associated with Acute Myeloid Leukemia (AML) disease and treatment and highlights understudied aspects of adult AML survivorship care, and potential novel areas for intervention.

Keywords: Acute myeloid leukemia; Cancer treatment; Hematopoietic; Survivorship

Introduction

The number of leukemia patients and survivors is growing. Acute Myeloid Leukemia (AML) is one of the most common types of adult leukemia, with at least 13,000 individuals diagnosed each year in the U.S [1]. The incidence increases with age, with 16.0 per 100,000 individuals age ≥ 65 years compared to 1.7 per 100,000 individuals age <65 [2]. The average age at diagnosis in the U.S. is 66 years old [3]. Approximately 60 to 70% of adult patients (aged 18-65 years) will achieve complete remission (CR), with 50-70% of first CR patients relapsing within 3 years. Approximately 22.6% of adult AML patients survive to five years [3]. Though there are relapses beyond this time period [4], most 5-year survivors are considered cured [5,6].

Proposed phases of cancer survivorship include the acute survival phase that begins with diagnosis and extends through therapy, the extended survival phase that begins when the patient goes into remission or has completed treatment, and the permanent survival phase which equates to cure, typically years after remission [7]. In this review, "survivor" refers to patients in the extended and permanent survival phase who have completed AML treatment and are in CR.

Adult AML survivors who achieve CR after enduring rigorous months of induction and consolidation therapy suddenly transition into a period of "watchful waiting"— integrating back into life while not knowing if and when their cancer may recur. Survivors also face disease and treatment sequelae manifesting as medical complications, deficits in quality of life and function, and persistent symptoms.

Medical providers are tasked with helping AML survivors transition from intensive treatment to disease monitoring and navigate the challenges of long-term survivorship. A number of questions arise when considering survivorship care for this population: What health-related quality-of-life (HRQOL) and medical complications are associated with AML disease and treatment? What are some novel interventions on the horizon that may be promising for disease surveillance and risk stratification? What areas of survivorship care require ongoing exploration?

Health-Related Quality-of-Life and Supportive Care Needs Beyond Cancer Treatment

Health status as defined by the World Health Organization is "a state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity," [8] and is comprised of inherited genotype and its phenotypic expression, functional condition, mental condition, and health potential. Quality of life is personal and subjective, and can be affected by and have overlaps with the health status of the individual. A person's quality of life encompasses political, societal/environmental, familial, and health system factors, while Health Related Quality Of Life (HRQOL) focuses on the effects of health care, illness and treatment on quality of life.

Impact of AML and its treatment on HRQOL

Studies of AML survivors include wide variations in demographics, modes of treatment, follow up time period, instruments used for outcome assessment, and with few exceptions, small sample sizes [9]. However, two general trends emerged.

First, AML and its treatment affect multiple QOL domains, particularly physical, psychological, emotional and sexual aspects. Second, most studies found significant deterioration in QOL shortly after diagnosis and during initial treatment, with subsequent improvement as time progressed. For example, in 1998, Schumacher et al followed 28 AML patients during inpatient treatment (for approximately 34 weeks), and found significant improvement in physical, role, social, and emotional function from start of induction therapy to the end of inpatient care using the EORTC QLQ-C30 QOL instrument [10].

The limited body of studies that evaluated QOL for long-term survivors suggests patients generally return to a satisfactory level of physical well-being, psychological and emotional state, though with ongoing challenges in sexual well-being [11-14]. There is significant HRQOL improvement between initial diagnosis and completion of treatment, but in some studies no further improvements were seen during the one or two year follow-up period post treatment [15,16].

More recently the AML 10 trial and the German AML-Intergroup conducted a cross sectional survey of AML survivors 1 year from the end of treatment and at least 5 years from CR, respectively [17,18]. Of the 481 patients in the AML 10 trial, measured at 1 year, most patients reported problem with emotional (75%), social (56%), cognitive

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functioning (53%), and many with problems in physical (41%) and role functioning (35%). These problems did not resolve, as the overall rates of patients who reported problems were higher in the German AML-Intergroup study, reported at least 5 years in CR, compared to the AML 10 study of survivors 1 year out.

While one's ability to draw conclusions from comparing different cohorts of AML patients between studies is limited, these findings raise the possibility that for certain survivors, their HRQOL trajectory with each passing year from CR may not improve, but plateau or even worsen. How do we identify adult AML survivors who are at higher risk for worse HRQOL, and what are potentially targets for intervention?

Potential target: survivors who underwent allogeneic stem cell transplant

In the EORTC-GIMEMA AML 8A trial and the UK MRC AML 10 trial, patients who received allogeneic bone marrow transplant (AlloSCT) had more negative HRQOL dimensions compared to those receiving autologous-bone marrow transplant (AutoSCT) and/or conventional chemotherapy. In the AML 8A trial, Zittoun et al. surveyed 98 patients in first CR for 1-7.4 years (median time of 53 months). Participants reported significant differences in physical functioning ('Do you have any trouble in taking a long walk?'), role functioning ('Are you limited in doing either your work or doing household jobs?'), and sexual functioning. AlloSCT was worse than AutoSCT, and chemotherapy better than both groups. A similar pattern was observed for overall physical condition and QOL ratings. AlloSCT participants also reported more symptoms of fever, mouth sores, dental problems, hair loss, headache, pain during sexual intercourse, and recent acute disease compared to AutoSCT and chemotherapy groups. No difference between the treatment groups was observed for symptoms of pain, nausea/vomiting, lack of appetite, and fatigue. After adjusting for time interval between achieving CR and QOL evaluation, there was no trend towards improvement as time interval increased except that mouth sores diminished [11].

Similar to the AML 8A trial, AlloSCT patients in the AML 10 trial suffered more than AutoSCT and chemotherapy-only patients in their global health/QOL ratings, sexual relationships, fertility, social relationships, professional activities, financial status, physical functioning and symptoms (mouth dryness, eye dryness, coughing, nausea/vomiting, fatigue, and GVHD-like symptoms) [12,18]. The German AML-Intergroup's cross-sectional study looking at people with at least 5 years of relapse-free survival after first-line treatment also showed more HRQOL deficits among AlloSCT than with chemotherapy-alone cohort [17].

Area for further study: Available literature highlights how AlloSCT patients report worse HRQOL in several domains compared to other post-remission strategies. It will be informative to tease out the key contributors to worse QOL so to devise targeted interventions. For example, recently, a cross-section study specifically surveying post-transplant patients found that risk factors for distress (on the Distress Thermometer) among AlloSCT respondents included younger age, shorter time after transplantation and GVHD [19]. Being aware of poor QOL risk factors will help the medical community better identify those at risk and devise upstream interventions. Further QOL studies can also better tailor patient/caregiver education programs. For example, focus groups exploring what post allogeneic transplant patients wish they had known about quality of life prior to transplant found majority of suggestions centered on education of late transplant complications [20]. In general, long-term prospective follow-up studies of this population will be able to provide much needed information [5]

Syrjala et al. [6] provides an example for such a study. They prospectively followed 319 lymphoma or leukemia patients, and assessed their function from before transplantation to 5 years after Hematopoietic Cell Transplantation (HCT). Ninety-nine participants survived to 5 years with no recurrence and 94 completed the 5-year follow-up assessment. Physical recovery was found to occur earlier than work or psychological recovery. Patients with slower physical recovery were more depressed and had higher medical risk prior to transplant. Patients with chronic GVHD, less social support before HCT, and women were more likely to be depressed after transplant [21]. An additional prospective study of survivors post allogeneic transplantation is underway where a series of patient-reported outcome measures will be collected [22].

Potential target: fatigue

The presence of physical symptoms predicts worse QOL. Fatigue is one of the most common symptoms among AML patients, even after controlling for the effects of anemia. Among older adults (60 years and over) receiving chemotherapy, fatigue scores had moderate to strong correlations with global health, physical, role, emotional, social, and cognitive function. Moderate and strong correlations were seen between fatigue and depression scores throughout all times points of the study [23]. In another study of inpatient AML treatment, fatigue on the EORTC QLQ symptom scales was the strongest predictor of worse physical and emotional functioning [16]. One year after completion of therapy fatigue scores improved by about 50%. However, fatigue remains a persistent problem. In the AML 10 trial, 1 year after achieving CR, 79% of patients reported problems with fatigue.

Area for further study: More studies are needed to explore the relationship between fatigue and QOL, biologic mechanisms of fatigue, pharmacological and non-pharmacological interventions, and the relationship between fatigue and other cancer symptoms such as cognitive impairment, anxiety, sleep disturbances, and depression.

Preliminary studies explored the biologic mechanisms of fatigue in an AML population assessing the correlations between fatigue scores, quality of life, and circulating cytokine levels. Panju et al. found IFN-γ, IL-2, IL-5, IL-8, and TNF-α correlated with global QOL scores and IL-5, IL-6, and IL-10 correlated with fatigue scores [24], Myeres et al. found correlations between levels of IL-6, IL-1 RA, and TNF-α to fatigue and overall QOL ratings [25]. Most recently, Fung et al. reported correlations between fatigue, TNF-α, and interferon-inducible protein-10 for AML patients before and after the first cycle of induction chemotherapy [26,27]. Studies to determine the biochemical relationships (causal versus epiphenomena), and interventions, are needed.

Successful [28-30], and unsuccessful [31,32] pharmacologic treatments of cancer-related fatigue are available, but no studies have targeted AML survivors [33]. Nonpharmacologic behavioral interventions are attractive alternatives to adding more medications to patients' often extensive pharmacopeias. Exercise and psychosocial therapies are among the better researched methods among cancer populations. Less well studied interventions include yoga [34], mindfulness-based stress reduction [35], nutritional therapy, sleep therapy, energy therapy, and restorative therapy, but none have been done in AML. Most studies were done among breast, prostate and colorectal cancer patients, with occasional lymphoma populations [36].

In recent years there has been increased interest in utilizing exercise for cancer survivors to improve fatigue and other HRQOL domains. A recent Cochrane review indicates that exercise may improve

fatigue, body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, and pain for cancer survivors [37]. Specifically within the adult AML population, the few available studies focus on the induction therapy timeframe and are of small samples size. Chang *et al* conducted a walking intervention (n=11), resulting in lower levels of fatigue scores and interference, symptom distress, anxiety, and depression [38]. Another exercise intervention study prescribed combined aerobic and strength training. Of the 8 patients, there were significant reductions in total fatigue and depression scores from baseline to post-exercise, with non-significant changes in QOL [39]. Alibhai also demonstrated the feasibility and safety of an exercise intervention among adult AML in-patients undergoing induction chemotherapy [40]. These studies lay the foundation for large randomized trials during the active treatment period, and hopefully will stimulate interest in studying exercise among long-term AML survivors. In most other areas of cancer treatment, it has become routine to recommend structured exercise throughout the treatment period based on multiple positive randomized trials [37,41].

Prior studies have also pointed out the associations between fatigue, sleep disorders, cognitive impairment, and depression in patients with other types of cancers [42-45]. It will be informative to explore the association between these symptoms in AML survivors, and whether intervention on one symptom has effect on the others.

What Medical Complications are Associated with AML Disease and Treatment?

While we discuss medical complications and HRQOL as separate concepts, it is important to acknowledge that this is an artificial divide. Due to the interplay between health status and quality of life, we oftentimes see overlaps between the two spheres.

Hematopoietic stem cell transplant

There is a growing body of work on medical complications post-transplant. The Bone Marrow Transplant Survivor study, a retrospective cohort study of hematopoietic cell transplantation (SCT) survivors for 2 or more years, studies late effects post-transplant [46]. Of the 673 eligible SCT survivors, 584 (87%) were contacted and 401 (69%) participated in the questionnaire. Of the respondents, the median age was 36.5 years, and AML was the predominant survivor group (70%). Overall, only 34% of survivors reported no chronic conditions, 38.2% reported impairment in more than one and 24% had impairments in more than two organ systems. Chronic graft-versus-host disease (cGvHD) was reported by 47% of AML survivors in this cohort [46], Baker et al. also looked at clinical and demographic predictors of organ system impairments for all SCT survivors and found AlloSCT therapy, especially with cGvHD, to be a predictor for several organ impairments.

Based upon existing information on late complications, detailed guidelines and screening recommendations for survivors post SCT are available [47,48] and continue to evolve as new information emerges. Here, we want to highlight two areas of post-transplant care: sexual health and cardiovascular risk evaluation.

Several studies documented an adverse impact on sexual functioning and fertility in the setting of SCT [12,17], Watson et al. surveyed 479 patients in the UK MRC AML 10 trial who were in their first CR for at least one year. In this cross-sectional study, significantly more SCT patients reported worse adverse effects on sexual health than chemotherapy-only patients. Comparing SCT with chemotherapy-only participants, SCT participants reported decreased interest in sex (48% vs. 24%), sexual activity (53% vs. 35%), pleasure from sex (36% vs. 18%), and ability to have sex (38% vs. 18%). In this study sample, 27% of participants believed their infertility was due to treatment, with significantly higher rates among SCT patients (AlloSCT 64%; AutoSCT 51%; Chemotherapy 10%) [12]. Patients and partners are not always comfortable voicing their issues with sexuality. Knowing the high prevalence of sexual dysfunction, particularly among AlloSCT patients, care providers can initiate the conversation and normalize the topic as part of routine survivorship care, as it is with breast cancer [49] and most other cancers [50].

Increased risk of developing cardiovascular risk factors and subsequent cardiovascular disease is another area of growing interest for survivorship care post-SCT. In a large retrospective cohort study of SCT patients at City of Hope, the prevalence of cardiovascular risk factors (hypertension, diabetes, and dyslipidemia) was significantly higher among AlloSCT recipients compared to the general population. Risk factors for developing these conditions include older age, obesity, history of grade II-IV acute GvHD, and total body irradiation. Cumulative incidence for cardiovascular disease (myocardial infarction, symptomatic coronary

artery stenosis, stroke, congestive heart failure) was 7.8% at 10 years after transplant, with a two- to threefold increase in cardiovascular-related deaths for long-term survivors compared to the general population [51,52]. Participants with multiple cardiovascular risk factors and pre-SCT cardiotoxic therapies were at highest risk for developing cardiovascular disease [53]. In a retrospective study of 109 long-term AlloSCT survivors (>5 years), men had significantly increased cardiovascular risk, with an approximate doubling in the 10-year risk of developing a cardiovascular event at 5 years after SCT, with persistently elevated risk at 10 years [54].

These data emphasize the importance of assessing cardiovascular risk in this population and practicing appropriate risk reduction interventions. They also highlight the role of developing novel screening strategies to better identify at-risk individuals.

For example Jain et al. , conducted a single center prospective non-randomized study using contrast enhanced cardiac computed tomography (CCT) for identifying post AlloSCT survivors at risk for cardiovascular disease via coronary calcium scoring (CCS). Of the twenty asymptomatic participants, eight (45%) patients had non-obstructive coronary artery disease (CAD) and one (5%) had obstructive disease. Four of fifteen (26.6%) patients found to have CAD on CCT was considered "low risk" category by Framingham cardiovascular risk scores. In this preliminary study, CCS alone was 89% sensitive and 100% specific in identifying CAD [55].

We encourage future studies evaluating the role of imaging studies and/or serum markers in specifically screening and risk-stratifying post AlloSCT AML survivors.

In contrast to the growing body of literature for post-SCT patients, overall, there is limited published experience on medical complications of long-term survivors of AML who were treated with chemotherapy alone or with less-intensive treatment (such as azacitidine). Known long-term toxicities of intensive chemotherapy include cardiac complications [56,57], infertility [12], and secondary myelodysplastic syndrome (MDS)/AML [58].

The typical induction therapy usually involves anthracycline and cytarabine. Anthracyclines are a widely used class of cytotoxic agents in the treatment of multiple cancers. The major limitation in its use is cumulative and dose dependent cardiotoxicity, with decrease in

systolic left ventricular function [57]. In addition to congestive heart failure, other cardiac complications include valvular dysfunction and arrhythma. Risk factors for increased toxicity include advanced age and male gender [56,59].

While infertility is a much less reported adverse effect compared to bone marrow transplant recipients, it is a known complication of induction and consolidation therapies, leading to permanent oligoasthenozoospermia and amenorrhea in middle aged patients [60]. Finally, another serious long-term complication is therapy-related MDS or AML with available data in case reports [58,61].

In general, a better understanding of treatment and disease sequelae for the chemotherapy-only group is needed to formulate a standardized post-treatment care plan. While most of the long-term survivorship work has been on post-SCT survivors, it is also important to focus on those treated with other modalities (chemotherapy alone and less-intensive treatment) as the treatment and disease experience may differ between the groups. Prospective, longitudinal follow-up studies will be informative in developing preventive practices and screening tests for these groups of survivors.

Novel Interventions for Consideration

Studying AML long-term survivors can lead to novel intervention strategies for monitoring disease relapse and better understanding of survivors' immune health.

Monitoring for recurrent disease and minimal residual disease

Despite CR rates of approximately 60 to 70% of among adult patients (aged 18-65 years), majority of patients relapse within the first 2-3 years. While pre-treatment classification of disease biology by cytogenetic and molecular parameters [62] can help stratify survivors in remission into different groups based on relapse risk, direct measurement of remaining disease burden post-treatment in those patients in achieving a clinical remission may provide additional prognostic information. Within each cytogenetic risk class (favorable, intermediate, and unfavorable risk), MRD levels have prognostic significance for patients in remission, with MRD^- patients doing better than those who remain MRD^+ [63-65].

To date, MRD has not been prospectively integrated into AML survivor management due to uncertainty in timing of MRD screening, lack of standardized assays, and lack of validated prognostic MRD thresholds [65,66]. However, with sensitive assays and established thresholds, MRD testing may be able to: identify peri-transplant patients in CR who are at higher risk for relapse and may be candidates for escalated or additional therapy; detect "molecular relapse" through serial surveillance MRD testing in patients who have hematological CR for earlier therapeutic intervention; quantify disease and used as a biomarker to reflect efficacy of therapy [67,68]. This is an area of ongoing research, and it will be exciting to see how MRD can personalize relapse screening plan and whether early intervention in patients with MRD can reduce relapse rate and improve survival.

Immune health and routine vaccinations for survivors

Infectious complications are frequent during the treatment and post-treatment periods due to patients' immunocompromised state. Cytopenias, immunosuppression, and/or immune ablation result in weakened immune system that recovers gradually over months to years. Particularly at risk for slower reconstitution are allogeneic HCT recipients, survivors with GVHD, and those on chronic immunosuppression. Some experts are using T-helper lymphocyte (CD4) counts and CD4/CD8 ratios as surrogate markers of the completeness of immune reconstitution [48].

A more thorough understanding of immune health can also help us understand how soon adults can be successfully vaccinated and revaccinated after completion ont for AML. For example, in patients with hematological malignancies influenza infection has been reported to be a cause of significant morbidity and mortality [68,69]. However, much of the available evidence for influenza vaccination in patients with hematological malignancies, on which clinical guidelines must be based, is either anecdotal in nature and/or based on heterogeneous groups of patients, diagnoses and disease states [70-74]. A recent Cochrane systematic review of vaccination for prophylaxis of viral infections in patients with hematological malignancies noted that there was no evidence that influenza vaccination in patients with haematological malignancies lowered the incidence of influenza or mortality due to infection but that there was some evidence that it lowered frequency of lower respiratory tract infections (RR: 0.39, 95% CI 0.19 to 0.78, P=0.008) and the rate of hospitalization (RR 0.17, 95% CI 0.09 to 0.31, P<0.00001) [75]. Comprehensive and detailed analysis of the immune system pre- and post- vaccinations can help elucidate the optimal timing for routine vaccinations among adult AML survivors and evaluate its effectiveness in prevention of infectious complications.

Being able to accurately assess survivors' immune health can have implications beyond guiding duration of infection prophylaxis and timing of vaccinations. Immune surveillance through T cells or natural killer cells may play a role in controlling residual disease. Patients with a swift and the highest T cell recovery within six weeks of chemotherapy have the lowest relapse rate [76-78]. This raises the question of whether a healthier post-treatment immune system can provide a more robust relapse surveillance.

Focus on special populations

Older adults: There is limited information available for HRQOL of older survivors (over age 60 years) in CR. Large cross sectional QOL studies from the AML 8A, AML 10, and AML-Intergroup trials consist mainly of younger adults, with the median ages of 44, 39, and 41 years, respectively. The biology of the disease differs between the older and younger cohorts -- older AML patients are more likely to have unfavorable cytogenetics [79,80], antecedent hematologic disorder, and treated with cytotoxic chemotherapy for prior malignancies [81]. Rates of disease free survival and CR are also lower for the older patients [82]. The added complexity of heterogeneity in performance status among older adults makes standardizing AML treatment for this group of patients a challenging endeavor. It may be helpful to utilize a "risk-of-treatment" stratification, weighing the potential short-term and long-term benefits and harms of different treatment options to a patient's quantity and quality of life [83].

Saini et al. recently reviewed the quality of life issues in elderly AML patients and highlighted the knowledge gaps in this population [84].

Supportive Care Needs for Caregivers

While some long-term survivors return to a satisfying level of health with minimal to no deficits in physical, psychological, social, and spiritual domains, others exchange an acute illness for a chronic disease. Among survivors that experience ongoing limitations and require ongoing caregiver support, caregiving can be viewed as chronic stress exposure. Heavy caregiver responsibilities in other diseases have

been associated with increased rates of depression, lower self-rated health, worse self-care, increased chronic illnesses, and increased mortality [85,86].

Cancer itself can have a profound impact on partners and close family members, including anxiety [87], fear of recurrence [88], worse quality of life [88], and unmet needs [89,90], Partners and family members' cancer experience can also differ from that of patients'. A study compared health status and supportive care needs of longer-term gynecological, breast, prostate and colorectal cancer survivors (1-11) years post diagnosis, mean (4.2 years) and their partners. Partners not only reported higher levels of anxiety and supportive care needs, they also had unique needs separate from the patients [91,92]. It is important that future studies look closely at the health status, psychosocial well-being and unmet needs of survivors' partners, caregivers, and family members.

AML remains one of the more common hematologic malignancies among adults. For survivors who achieved complete remission after months of rigorous treatment, they enter yet another time of physical, emotional, social, and role adjustment. As patients live through the first months of watchful waiting to decades of disease remission, being knowledgeable of the medical and QOL sequelae will enable us to provide them with targeted survivorship care and help them lead fuller and healthier lives.

Conclusion

The impact of AML and its treatment on HRQOL as well as medical complications related to the disease and therapy is substantial. These survivors experience some immediate gains in health but most have substantial symptoms such as fatigue and sexual dysfunction. Survivors are at high risk compared to the general public or their siblings for heart disease and vascular complications.

We highlighted several areas for further investigation, including:

- Management and treatment of fatigue.
- Impact of exercise on survivor's health and well-being.
- Long-term medical complications and QOL for survivors treated with chemotherapy-alone.
- The role of MRD testing
- Survivors' immune profile and its impact on timing of vaccinations and disease recurrence. Focus on QOL and treatment challenges unique to older patients with AML.
- Identify supportive

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