Time spent in complete remission (CR) and overall survival (OS) in AML patients.

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Abstract

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Table of contents

LIST OF TABLES

LIST OF FIGURES

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Introduction:

In 1961, Freireich *et al* demonstrated that patients with acute myeloid leukemia (AML) who achieve complete remission (CR) live longer than those who do not and that the difference in survival is accounted for by the time spent in CR. And now after 50 years of advances in medicine-new technology, new chemotherapeutic drugs, and especially supportive care-is this still true that the longer survival is contributed to the time spent in CR. Requirements for CR included the presence of less than 5% abnormal blasts in the bone marrow, the absence of extramedullary AML,and recovery of neutrophil and platelet counts to greater than 1,000/_L and greater than 100,000/_L in the peripheral blood.

Our questions are:

1-Does CR prolong survival or does CR only denote patients more likely to live longer?

2- See what proportion of survival time spent in CR: greater proportion more likely CR contributed to survival.

3-Is the longer survival explained by the fact that majority of the survival time is spent in CR?

Literature Review

Acute myelogenous leukemia (AML) is an aggressive form of blood cancer in which too many normal myeloid blood stem cells become abnormal leukemic cells. Other names for this disease are acute myeloid leukemia, acute myeloblastic leukemia, acute granulocytic leukemia and acute nonlymphocytic leukemia. The term “acute” means that this disease progresses quickly, and if it is not treated, it can be fatal within a few months. This disease typically affects older people. The average age at diagnosis is 67 years old, although about 25 to 30 % of patients are younger than age 50. AML is slightly more common in men than women. The lifetime risk of being diagnosed with AML is about 1 in 250 for a man and 1 in 300 for a woman (American Cancer Society, 2009). Leukemia is a cancer that disrupts the normal development of blood cells. Inside most of the bones is a soft spongy material called bone marrow in which blood stem cells (immature blood cells) are produced. A blood stem cell becomes one of two types of stem cells: myeloid or lymphoid, which mature into different kinds of blood cells. Acute myelogenous leukemia (AML) disrupts the normal development of myeloid

stem cells. With AML, myeloid stem cells turn into leukemic cells (also calls blasts) that multiply very quickly, lose the ability to differentiate normally and to respond to normal regulators of proliferation. AML blasts also inhibit normal blasts from differentiating into mature progeny. Inhibition does not result from "crowding out" of normal blasts because there is no correlation between degree of cytopenia and marrow blast count; rather inhibition may be mediated by various chemokines produced by AML blasts. In AML immature cells (cancer cells) accumulate in the bone marrow. These leukemic cells do not mature or function like normal blood cells, and do not 'die off as normal cells should. As a result, these leukemic cells begin to accumulate and because of their failure to mature lead to a reduced number of normal blood cells, which in turn can cause infection, anemia, and excessive bleeding. And these leukemic cells move out of the bone marrow and into the bloodstream where they can disrupt other parts of the body, including the liver and spleen, mouth and gums, and the central nervous system.

Patients die because of disease complications as a result of marrow failure. The principal sign of marrow failure in AML is infection. AML can be *de novo* (ND1) or it can be secondary (ND2) as a result of antecedent hematologic disorder (AHD), or as a result of prior cytotoxic therapy or exposure to ionizing radiation, benzene, and cytotoxic chemotherapy. Elderly patients have poor outcomes as compared to young adults (Estey 2012) (National Marrow Donor Program, 2009).

It may be possible to make the diagnosis on the basis of a peripheral blood examination; nevertheless, a bone marrow aspiration is strongly recommended. The flow cytometry is used to evaluate minimal residual disease (MRD) (Cheson BD, et al 2003). According to WHO criteria, a myeloid neoplasm with 20% or more blasts in the PB or BM is considered to be acute myeloid leukemia (AML) when it occurs *de novo*, evolution to AML when it occurs in the setting of a previously diagnosed myelodysplastic syndrome (MDS) or myelodysplastic/ myeloproliferative neoplasm (MDS/MPN), or blast transformation in a previously diagnosed myeloproliferative neoplasm (MPN). At least 20% of the blasts must have surface antigens associated with myeloid differentiation, most commonly CD33 or CD13. The are some special cases of AML diagnosis: if more than 80% of the marrow comprises monocytes, acute monocytic leukaemia is diagnosed; if more than 50% of the marrow consists of normoblasts or pronormoblasts and if myeloblasts constitute more than 30% of the non-erythroid population, the diagnosis is erythroleukaemia; and

if the marrow is inaspirable, a diagnosis of megakaryocytic leukemia should be considered, with the diagnosis confirmed by biopsy. A tumoral proliferation of blasts in an extramedullary site (myeloid sarcoma) is also considered to be AML when it is found de novo or in a patient with MDS or MDS/MPN, and blast transformation in cases of MPN.

Blast percentages should be derived, when possible, from 200-cell leukocyte differential counts of the PB smear and 500-cell differential counts of all nucleated BM cells on cellular marrow aspirate smears stained with Wright-Giemsa. Although a BM core biopsy may not be required in every case, an adequate biopsy does provide the most accurate assessment of the marrow cellularity, topography, stromal changes, and maturation pattern of the hematopoietic lineages, and it can be invaluable in detecting residual disease following therapy. A complete cytogenetic analysis of BM cells is essential during initial evaluation for establishing a baseline karyotype; repeat analyses are recommended as needed thereafter for judging the response to therapy or for detecting genetic evolution (Vardiman et al.2009) (Estey et al.2006).

Treatment: For the past 30 years, treatment of AML has generally consisted of the combination of an anthracycline, such as daunorubicin or idarubicin, and cytarabine. Therapy consists of two phases. The first attempts to produce complete remission, defined as a marrow with less than 5% blasts, a neutrophil count greater than 1000, and a platelet count greater than 100 000. Complete remission is the only response that leads to cure and, at the least, to an extension in survival. The second phase of therapy aims to prolong the complete remission. Once a patient has been in remission for three years, the likelihood of relapse declines sharply to less than 10%.

Treatment of elderly patients: Although each additional year beyond age 18 is associated with poorer prognosis, patients with AML are thought of as elderly from age 55–60 years. To some extent, poor outcomes in elderly patients are associated with the factors predicting early death and, in particular, resistance to therapy. However, even after accounting for these factors, old patients have worse outcomes than young patients. This finding reflects the effect of unknown genetic and biological markers.

Standard versus investigational therapy: Three general options are available for management of elderly patients: standard treatment, (e.g., with 3+7 followed by three to six courses of the same drugs at lower doses to maintain the remission), investigational treatment, and palliative care. Investigational therapies are those that have not received general approval for standard use, for example clinical trials. Finally, palliative care is also referred to as supportive care, where patients receive treatments to ameliorate symptoms with no intent to treatment the disease itself. An example of palliative care is blood transfusions for anemic patients. The median survival times of 10 months make it difficult to recommend standard therapy to many old patients. This is particularly so given the 15–20% risk of treatment-related death in the one-two month remission induction period (Estey et al.2006**).** Chemotherapy often goes hand in hand with lowered blood counts, increased symptoms, and a high risk of infections. Furthermore, chemotherapy targets proliferating cells; meaning it can destroy tumors but not stem cells, thus cancer can recur. Instead, hematopoietic stem-cell transplantation (HSCT) offers the only possibility for a cure, although curative rates are still low.

HSCT:

The rate of complete remission for adults with acute myeloid leukemia is approximately 65 % overall and decreases with increasing age and the presence of unfavorable cytogenetic abnormalities. With post remission therapy, disease-free survival at five years ranges from 10 to 15 % with low-dose maintenance therapy to 25 to 35 % with intensive courses of chemotherapy, usually incorporating high-dose cytarabine. In young patients, further escalation of post remission therapy is feasible, provided autologous or allogeneic hematopoietic stem cells can be transplanted to repopulate the ablated bone marrow. Despite the complications of graft-versus-host disease, a number of studies suggest that long-term outcome is improved by allogeneic marrow transplantation during the first complete remission (Cassileth PA et al 1998).

Hematopoietic cell transplantation (HSCT) is an effective therapy for AML. Obstacles to broad applicability of HSCT therapy for the majority of patients with AML have included inability to control leukemia with primary induction therapy, lack of suitable hematopoietic cell donors, toxicities of HSCT conditioning regimens and long-term complications of the transplant procedure. While all anti leukemia therapies are complicated by the problems of chemotherapy-related toxicities and disease relapse, allogeneic HSCT also

exposes patients to the risks of potential failure of engraftment; organ toxicities caused by GVHD and prolonged immunosuppression with its attendant risks of post-HSCT infectious complications.

In the last decade, several developments have made allogeneic HSCT a more "user-friendly" treatment modality. Expansion of the pool of donors in national and international registries as well as the establishment of cord blood banks has vastly increased the likelihood of success in identifying a suitable HLA match for patients who lack matched family donors. Improvements in post-transplant supportive care and the development of newer immunosuppressive agents have also had an impact on transplant-related toxicities. More refined PCR-based screening for cytomegalovirus reactivation allows pre-emptive therapy tailored to viral load. New less toxic antifungal agents such as voriconazole and caspofungin have decreased early mycotic infections and make it feasible to provide long-term fungal prophylaxis in patients at high risk due to chronic GVHD.

New immunosuppressive agents, such as sirolimus and mycophenolate mofetil (MMF) are being incorporated into GVHD prophylactic regimens to decrease the incidence of acute and chronic GVHD in high-risk populations including unrelated donor recipients and older (> 50 years) patients. The change that may have the greatest impact, however on AML treatment is the advent of reduced intensity or non-myeloablative HSCT. Reduced-intensity HSCT relies upon the graft-versus-leukemia effect of the allograft rather than the direct tumoricidal activity of the conditioning regimen. Because of the paucity of any direct antileukemic effect of the conditioning regimens, the truly non-myeloablative (NMABT) regimens can only be used in patients with low volumes of disease, whereas the reduced-intensity conditioning regimens, which usually contain fludarabine and some alkylating agent, do have direct antileukemia activity and can be used with more extensive disease. The shortened duration of cytopenias and the minimal mucosal toxicity of the newer reduced-intensity conditioning regimens provide a reasonably safe transplant option for patients two decades older than the population that was treated with traditional fully ablative high-dose chemoradiotherapy regimens (Stone RM et al.2004).

Prognostic factors: Prognostic factors can be divided into those associated with treatment-related death occurring before response can be assessed and those associated with

resistance to treatment. The main predictor of treatment-related death is the patient's performance status on the Zubrod scale. Age, serum albumin, bilirubin, and creatinine and various indices of morbidity, are other predictors of early death, with each probably independent of each other as well as of performance status.

Effect of age: Older patients with AML are most often presented with lower performance status and higher number of co-morbidities, which significantly reduces their likelihood of having the desired response to chemotherapy as well as their transplant outcomes (Appelbaum, Gundacker, Head, et al., 2006; Atallah, Cortes, O'Brien, et al., 2007). For example, the complete response rate for patients between 55 and 70 average around 45% and decreases significantly to 25% of patients over 70 years old (Appelbaum, 2006).

Effect of cytogenetic: About 55% of adults have cytogenetic abnormalities at diagnosis. The importance of cytogenetic characteristic as a prognostic factor has been recognized by the World Health Organization in their revision of the classification of AML to include it as a parameter. Various studies have suggested that cytogenetic abnormalities found at disease diagnosis are key prognostic indicators in AML, specifically in regards to response to induction and consolidation chemotherapy (Grimwade, Walker, Oliver, et al., 1998; Ferrant, Doyen, Delannoy, et al, 1995; Mrozek, Heinonen, de la Chapelle, Bloomfield, 1997; Samuels, Larson, Le Beau, et al, 1988). Patients who had monosomal karyotype positive (MK+) were associated with the highest incidence of relapse.

Cytogenetic findings permit patients' risk to be categorized as favorable, intermediate, or adverse—with very different cure rates. However, there is substantial variability in outcome, particularly within the intermediate and favorable groups (Estey et al.2006) (Estey 2012). In addition to the classification of AML patients by their cytogenetic abnormalities; molecular genetic studies in the last ten years have also identified important clinical and biologic subsets of AML patients. Two prominent examples, both associated with a poorer prognosis in AML patients with normal cytogenetics, are (1) internal tandem duplications of FLT3 mutations and (2) partial tandem duplications of the MLL gene on 11q23. Identification of patients with specific molecular genetic abnormalities may be important as therapies targeted to these molecular genetic lesions are developed (Cheson BD, et al)

Effect of remission status.

A variety of treatment outcomes (Table-1) are used to measure the effectiveness of treatment regimens in clinical trials for AML. Two important categories of outcome are indicators of response to therapy and measures of the duration of survival or remission. Duration of survival or of response is measured from a defined starting point (e.g., the date of entry onto the study or the date of response) to the end point of interest (e.g., death or AML relapse). Such time-to-event data are characterized by the possibility of censoring (i.e., by the possibility that the end point of interest will not be observed for some patients because of the end of study follow-up) or because other intervening events (so-called competing events) preclude the end point's occurrence.

Table 1:Definitions of End Points in AML

Outcomes	Response Category	Point of Measurement	Definition
Overall survival	All patients	Date of AML Diagnose	Death from any cause
Relapse-free survival(RES)	CR	Leukemia-free state	Disease relapse or patient death from any cause
Remission duration	CR	Date of CR	Disease relapse

Overall survival is defined for all AML patients as measured from the date initial diagnose of AML until death from any cause. For a patient who is not known to have died by the end of study follow-up, observation of OS is censored on the date he or she was last known to be alive. Defined in this way, OS is ordinarily not subject to competing risks in clinical trials, and the product limit method of Kaplan and Meier can be used to calculate estimates of survival probabilities.

Relapse free survival (RFS) is defined only for patients who achieve CR, and is measured from the date of attaining the leukemia-free state (as discussed previously) until the date of AML relapse or death from any cause, whichever occurs first. For a patient who is not known to have relapsed or died by the end of study follow-up, observation of RFS is censored on the date of his or her last follow-up examination.

Remission duration, like RFS, is defined only for patients who achieve CR, and is measured from the date of CR by blood count recovery and bone marrow examination (rather than the date of the confirmatory bone marrow), until the date of relapse. However, unlike DFS, it is measured only until the date AML relapse is detected. For patients who die without report of relapse, remission duration is censored on the date of death, regardless of cause. For a patient with no report of relapse by the end of the follow-up data collection, observation is censored on the date of his or her last follow-up examination. Note that unlike OS, EFS, and RFS, remission duration is subject to the competing risk of death without relapse. Therefore, the Kaplan-Meier method does not provide estimates of probabilities of remaining relapse free, and estimates of the cumulative incidence of relapse (CIR) should be used instead.(Cheson et al. 2003).

Survival: According to the Leukemia & Lymphoma society, the five-year relative survival rate has nearly quadrupled in the past 48 years for patients with leukemia. From 1960 to 1963, the five-year relative survival rate among Americans of European descent with leukemia was 14 %. From 1975 to 1977, the average five-year relative survival rate for all persons with leukemia jumped to 35 %, and from 1999 to 2005 the overall relative survival rate was 54 %. The rate specific to AML patients between 1999 and 2005 is 23.4% overall and 60.2% for children under 15.

Disease survival is based on a variety of factors, such as individual characteristics, the age of diagnosis, co-morbidity conditions, the stage of AML, as well as the choice of treatment (Kroger et al., 2009). There has been a recent increase in interest in looking at survival differences between patients who are diagnosed with *de novo* AML and secondary AML. Although these two types of AML show a similar disease profile and are often treated similarly, the treatment outcomes of these patients differ greatly (Estey et al., 1997).

Although both presentations of AML display similar symptoms and are often treated similarly, their prognosis varies significantly. Mainly, secondary AML carries a poorer

prognosis: reported complete remission rate for standard induction therapy in this population can be as low as 3%, with an average of 28% for therapy related AML and 36% for MDS-related AML. Patients with a long history of MDS, complex abnormalities, del7q, or del5q experience the lowest remission rate. Relative to secondary AML patients, *de novo* AML patients achieve a higher rate of remission with conventional chemotherapy and the remission duration is often longer. The few patients who achieve remission through conventional therapy maintain the remission status for a short period of time and not without hardship.

Methodology:

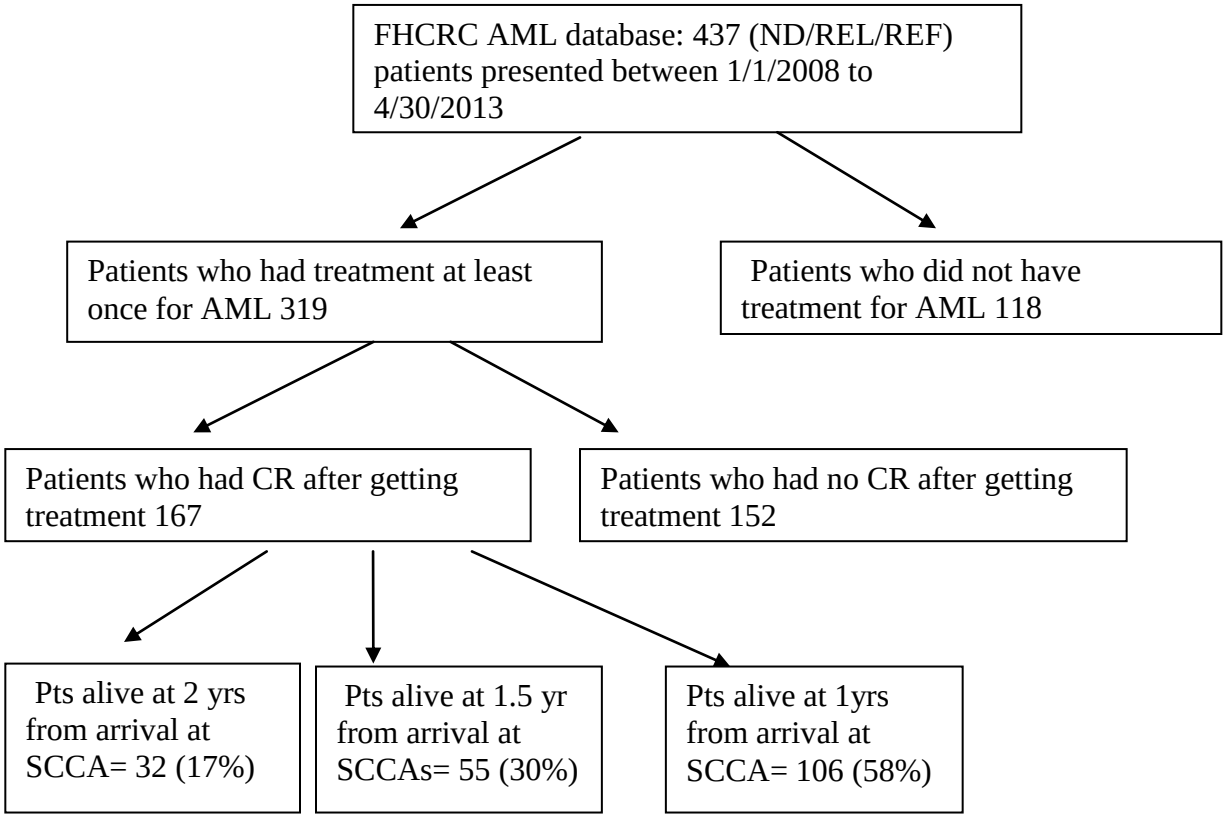
Selection of Subjects: The study population was selected from the AML database at the Fred Hutchinson Cancer Research Center (FHCRC). The AML database contains data from patients who are seen at the Seattle Cancer Care Alliance (SCCA) and the University of Washington Medical Center (UWMC) who provided consent to have their clinical information kept in the database for research purposes. The SCCA is an alliance organization of the FHCRC, UWMC, and Seattle Children's Hospital, each having equal ownership and contribution to the adult and pediatric medical oncology/hematology clinical care programs. Information about patient's diagnosis, treatment, relapse and survival is kept in the research database.

The Clinical/AML Research Data Systems department has several quality assurance processes in place. The first is data entry programs with pre-set validation within each key entry program. Examples of this include date range validation, where date that is in the future cannot be entered. Also, each key entry field may have its own set parameters where for instance you could not enter data that are outside the pre-set parameters. An example of this would be results of a CT scan cannot be entered under the biopsy event code. All key entry for each user produces a paper verification report that is given back to the person for them to review, to look for entries that seem to be outside the range, or seem to be incorrect. All final work is then passed onto a separate person for a second review. This person goes over the final print out and checks for any errors. If necessary, source documents are reviewed to resolve errors and discrepancies.

Collection of Data: (Figure 1) A formal query of the AML database was created to select a sample with the diagnosis of Acute Myeloid Leukemia (AML) age 60 years or above who presented between January 1, 2008 and April 30, 2013 at Seattle Cancer Care

Alliance/University of Washington Medical Center Leukemia Services. A review of the patients' diagnostic pathology report and physician's consult dictation was performed to separate patients into two groups based on their disease presentation: *de novo* AML and secondary AML. For patients who had secondary AML, information about their primary disease was also collected from the review. The patients' gender, age, survival status, relapse status, CR duration, WBC, transplant status, cytogenetic, molecular markers (FLT3), antecedent hematologic disorder (AHD), duration of AHD , extra medullary disease and number of chemotherapy were collected for all patients for final analysis.

Figure 1: Study population



IRB Review. This study was approved by the Fred Hutchinson Cancer Research Center Institutional Review board (IRB) on January 9, 2013 prior to data collection and analysis. As this is a retrospective chart review-only study with no planned contact of study participants, a request of a waiver of the requirement to re-consent was approved. The data to be used by this study are data that have been collected for diagnosis and treatment per standard procedures. All study activities are within the parameters of that waiver of consent approval.

Analysis

The following questions are being addressed in the present study:

1-Is there a difference in survival between AMLs patients who gets CR after getting chemotherapy compared to patients who never attain CR after chemotherapy? Does CR prolong survival or does CR only denote patients more likely to live longer?

2- What proportion of survival time is spent in CR?

3-Is the longer survival rate explained by the fact that majority of the survival time is spent in CR? There might be other factors associated with this patient population (who get CR) which prolong survival. For example these patients might be good risk patients to begin with who responded to therapy in contrast to patients who did not.

Variables used for analysis:

- **Age** at the time of diagnosis of AML
- **AML as ND1 (*de novo*), ND2 (secondary), Relapsed or Refractory** -Secondary AML is developed after exposure to cytotoxic agents or as a progression of an antecedent disease, such as myelodysplastic Syndrome (MDS). *De novo* AML refers to a spontaneous presentation not relating to previous disease or treatment.
- **SWOG Cytogenetic** is categorized as intermediate, unfavorable, miscellaneous and not done. We took out patients with favorable risk cytogenetic.

- Intermediate risk included normal cytogenetic, +8, +6, -Y, del(12p).

-Unfavorable included-del(5q)/-5,-7/del(7q), abn 3q,9q,11q,20q,21q,17p,t(6;9), t(9;22) and complex karyotypes(≥3 unrelated abn).

-Miscellaneous is all other abnormalities.

We excluded patients who had: t (8; 21)(q22;q22); *RUNX1-RUNX1T1*

-inv (16) (p13.1q22) or t (16; 16) (p13.1; q22); *CBFB-MYH11*

-Mutated *NPM1* without *FLT3*-ITD (normal karyotype)

-Mutated *CEBPA* (normal karyotype)

- **Treatment intensity**

Treatment which resulted in best response, if it was of high, intermediate or low intensity.

- **Response –definition of responses used were:**

-CR-Morphologic complete remission: A CR designation requires that the patient achieve the morphologic leukemia-free state and have an absolute neutrophil count of more than 1,000/_L and platelets of ≥100,000/_L. Patient must be independent of transfusions and no residual evidence of extramedullary disease.

-CRp- Morphologic complete remission with incomplete platelet recovery (CRp). All the criteria of the CR are fulfilled except for thrombocytopenia (< 100,000/_L).

-CRi-Morphologic complete remission with incomplete blood count recovery (CRi). All the criteria of the CR are fulfilled except for residual neutropenia (<1,000/_L) or thrombocytopenia (< 100,000/_L).

-MRD-minimal residual disease which means blasts by morphology are <5% but by flow cytometry blasts are >5%.

-**Refractory or treatment failure** is when blasts by morphology are >5% and counts haven't recovered - neutropenia (<1,000/_L) and thrombocytopenia (< 100,000/_L).

-**Morphologic relapse.** Relapse after CR defined as a reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow not attributable to any other cause (e.g., bone marrow regeneration after consolidation therapy). The appearance of new dysplastic changes also considered relapse.

Table-2 Responses in AML

Response	Bone Marrow blasts (%) by Morphology	Bone Marrow blasts (%) by Flow	Neutrophils (µL)	Platelets (µL)
CR	<5	<5	>1,000	>100,000
CR-MRD	<5	>5	>1,000	>100,000
CRp	<5	<5	>1,000	<100,000
CRp-MRD	<5	>5	>1,000	<100,000
CRi	<5	<5	<1,000	>100,000
CRi-MRD	<5	>5	<1,000	>100,000
REFRACTORY	>5	>5	<1,000	<100,000
N/A				

- **Survival in CR (of any kind)-**is the number of days the patient survives in each CR. Per policy, when a patient experiences a relapse or a death, the physician at SCCA or the UWMC is notified, and the data system is updated. The patients are assumed to be alive and still in remission unless otherwise noted..

Results:

Population Characteristics: Table 3 shows the characteristics of the study population.

One hundred and sixty seven patients got CR (of any kind) after getting treatment. After getting chemotherapy for AML patients were evaluated and remission status was determined (according to response criteria described above).

There were more males (64%), and the age range was 60-85 years. One hundred and three patients (62%) presented with secondary acute myeloid leukemia (AML ND2), 64 patients (38%) presented with primary AML (AML ND1).

Table 3-Study Population Characteristics	
Parameters	Pts got Rx. & had CR 167
Age range in yrs	60-85
Secondary AML ND/ND2	
ND1	64(38%)
ND2	103(62%)
Had HSCT after getting Dx. with AML	
HSCT Yes	68(41%)
HSCT No	99 (59%)
Extramedullary Disease	
Yes	8 (5%)
No	142 (85%)
SWOG cyto category	
Intermediate	95 (57%)
Miscellaneous	13 (8%)
Unfavorable	45 (27%)
Not Done	4 (2%)
Favorable	10 (6%)
P.S. at Initial Presentation	
0	6(4%)
1	126 (75%)
2	28 (17%)
≥3	7 (4%)
Gender	
Males	107 (64%)
Prior Hematologic Disorder	
MDS	33 (20%)
MPD	3 (2%)
Others (e.g. AHD etc.)	40 (24%)
None	88 (52%)
Unknown	3 (2%)
# of treatment	
1	107 (64%)
2	43 (26%)
3	14 (8%)
≥ 4	3 (2%)
WBC at presentation x10^3/uL	
Median (Range)	3.12 (0.21-117)
# of patients died	66(40%)
Duration of previous hemat. disorder	
Median (Range in month)	9 (1-132)

Cytogenetic characteristics were also assessed at initial diagnosis of AM L. A total of 95 patients (57%) had Intermediate cytogenetic, 45 (27%) had unfavorable cytogenetic, 13(8%) had miscellaneous cytogenetic and 4 (2%) did not have cytogenetic assessed. Seventy eight (41%) had a transplant, and 99 (59%) didn't have transplant after getting diagnosed with AML.

Table 4: CR1 Summary in patients who survived at 1.5yr (55)	
CR1 summary, N(%) reported	
CR	33(60%)
CR-MRD	10 (18%)
CRi-MRD	1 (2%)
CRp	3 (5%)
CRp-MRD	0 (0%)
Cri	3 (5%)
No CR	5 (9%)

Statistical Analyses

CR status and treatment intensity were tabulated and compared using Fisher's exact test. Time spent in CR in the first 1.5 years was tabulated and displayed with a histogram. All analyses were done with the statistical program R. R is a language and environment for statistical computing and graphics.

Table 4 shows of the best response patient had to the treatment and what percentage of patients had that specific response. The majority of patients who survived 1.5 years or more had complete remission (CR) (60%) and CR-MRD (18%). In contrast, among patients who survived 1.5 years. 9% did not get a remission. This indicates that patients who survive longer, the majority of them got CR or CR-MRD, which might have contributed to their longer survival.

Table 5 shows what kind of treatment/chemotherapy regimen patients got who survived 1.5 years or more. Majority of the patients got low intensity treatment 40%, followed by intermediate (32%) and high intensity (28%). This indicates that patients who survived 1.5 years or longer, majority of these patients got low intensity treatment. Low intensity treatment might be favorable as patients would suffer fewer treatment related toxicities.

Table 5: Treatment intensity Summary in patients who survived at 1.5yr (55)	
Treatment intensity summary(%) reported	
High	15 (28%)
Intermediate	17 (32%)
Low	21 (40%)

Table 6: CR1 and Treatment intensity Summary in patients who survived at 1.5yr (55)				
CR1 and Treatment intensity summary, N (%) reported				
	High	Intermediate	Low	P-value
CR	10 (30)	13 (39)	10 (30)	0.84
CR-MRD	3 (30)	2 (20)	5 (50)	
Cri-MRD	0 (0)	0 (0)	1 (100)	
CRp	1 (33)	0 (0)	2 (67)	
CRp-MRD	0 (0)	0 (0)	0 (0)	
Cri	1 (33)	1 (33)	1 (33)	
No CR	0 (0)	1 (33)	2 (67)	

Table 6 summarizes responses based on the intensity of treatment patients received. Majority of the patients who had CR got intermediate intensity treatment 39%, followed by both low and intermediate intensity treatment 30%. Patients who had CR-MRD, most of them received low intensity therapy 50%, followed by high 30% and then low intensity 20%. Patients who had CRp, 67% got low intensity and 33% got high intensity treatment. This table shows that patients who survived 1.5 years or beyond that had CR or CR-MRD and got low to intermediate therapy. This indicates CR/CR-MRD and low/intermediate treatment might contribute to longer survival.

Figure 2: Histogram of % time of _first 1.5 years spent in CR1,

Patients alive 1.5 years after FHCRC arrival

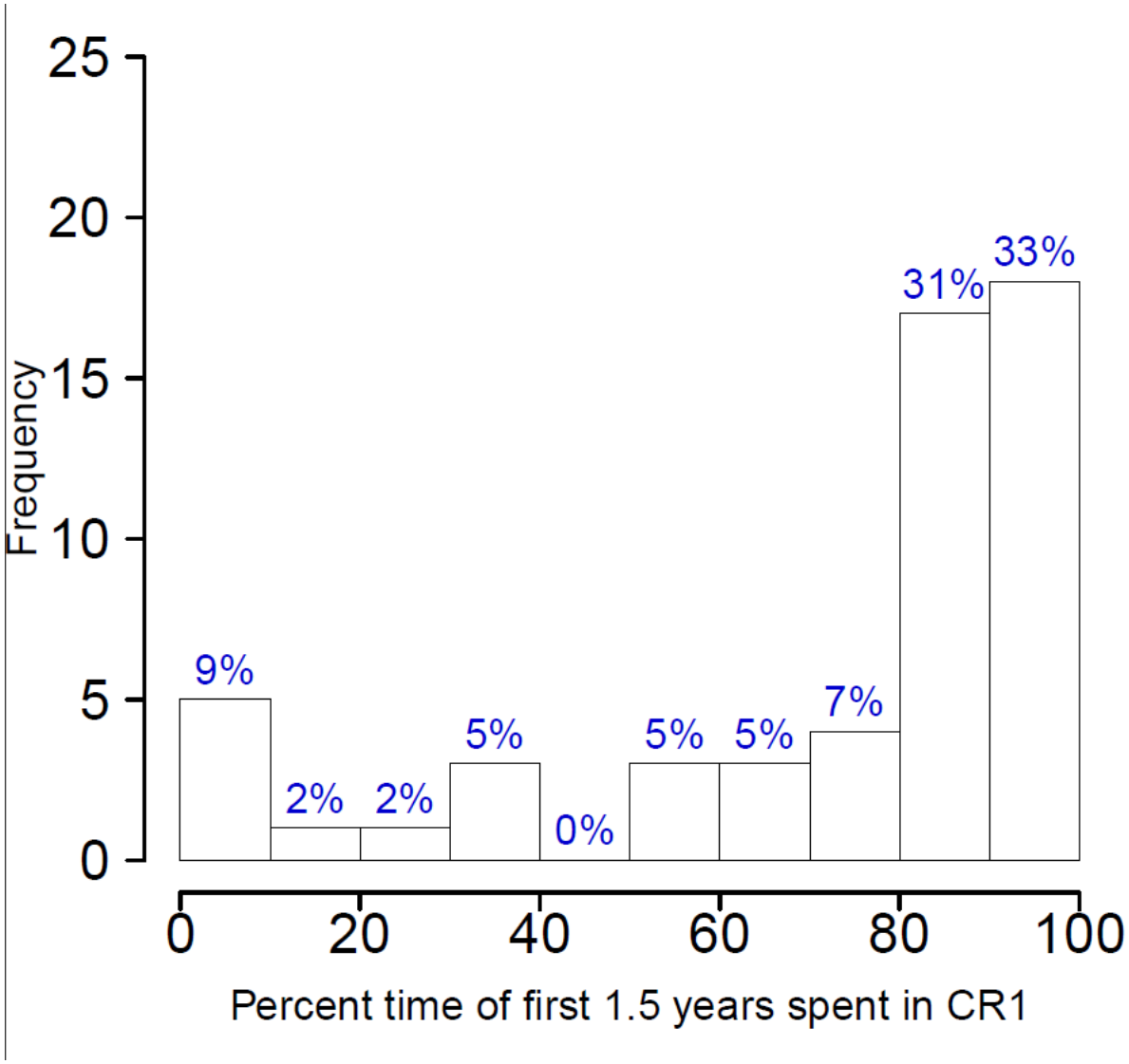


Figure 2 indicates that among patients who survived 1.5 years or longer, spent 64% spent more than 80% of their survival time in CR. This means for longer survival it is important to get response to chemotherapy.

Discussion:

In a retrospective study published in 2001 Freireich et al in 1961 found that patients who achieved CR lived longer than those who did not with the difference in survival time largely accounted for by time spent in CR. This suggested that CR itself was responsible for longer survival. Specifically most AML patients die with infection and patients in CR have, by definition, a neutrophil count high enough to greatly decrease the risk of infection. However in the 5 decades since this study was published supportive care for AML has improved greatly. In particular better anti-fungal antibiotics are available. Hence it is plausible that even without adequate numbers of neutrophils patients not achieving CR can live longer than before and that differences in survival between these patients and those achieving CR are much less than before. This possibility motivated our study.

Our results suggest however that CR is still very important for prolonged survival. Thus, table 4 indicates that 78% of patients alive at 1.5 years achieved CR. Furthermore, as seen in figure 2, 64% of patients alive at 1.5 years spent >80% of tis time in CR. On the other our data (table 2) suggest that the intensity of the treatment given to induce CR is much less important than whether CR is achieved. This observation provides a rationale for departing from higher intensity treatments, provided lower intensity treatments can produce a similar CR rate.

Our study has several limitations. Perhaps the most important limitation is small sample size. A second is that our population consisted of patients with both newly-diagnosed and relapsed AML. In general relapses are more common and occur quicker in the latter. Finally, our definitions of high, intermediate, and low intensity treatment, is arbitrary although clinically sensible.

In summary, our data suggest that getting remission (specifically CR) is very important in AML patients, because it is associated with better 1.5 year survival; and, most likely, improved overall survival. The survival data indicate that the group of patients showing the best response to chemotherapy had the best survival. This analysis suggests that chemotherapy has prolonged survival in AML patients. The improved survival time results from the high proportion of patients who did have a clinical response to therapy. Our data shows that the

improved supportive therapy with antibiotics, transfusions etc., has not significantly prolonged the survival of patients who fail to respond hematologically to chemotherapy.

Recommendations

Continued search both for new chemotherapeutic agents which can induce durable remission and for improved use of presently available therapy should be done in order to improve long term survival in people with AML.

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