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Retrospective Study

The Outcome of Outpatient Intermediate and High Dose Cytarabine Consolidation Chemotherapy in Patients with Acute Myeloid Leukemia. The Experience of King Fahad Specialist Hospital in Dammam, Saudi Arabia

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Keywords: Acute myeloid leukemia; Outpatient consolidation chemotherapy; High-dose cytarabine; Intermediate-dose cytarabine; Hematopoietic stem cell transplantation

Abstract

Background: Adult patients with Acute Myeloid Leukemia (AML) have traditionally been hospitalized for the duration of intensive consolidation chemotherapy until blood count recovery to avoid complications. Recently, there has been a trend to shift the care of AML patients treated with intensive chemotherapy from inpatient to outpatient settings to reduce treatment costs and save beds.

Methods and materials: A retrospective study of AML patients who received cytarabine consolidation chemotherapy between the 1st of August 2016 and the 31st of December 2023 at King Fahad Specialist Hospital in Dammam, Saudi Arabia was performed.

Results: Over a period of 7 years and 4 months, 62 patients received a total of 127 cycles of intensive consolidation chemotherapy at outpatient setting. At diagnosis: 12 patients had extramedullary disease, and 17 patients had adverse cytogenetic abnormalities. Following the 127 cycles of chemotherapy, 38 episodes of febrile neutropenia were encountered, and 46 hospital admissions were required. No complications were encountered following 62.2% of the cycles of consolidation therapy and no early mortality due to intensive consolidation therapy was reported. Out of 62 patients studied, 36 patients underwent various forms of hematopoietic stem cell transplantation. Disease relapses were encountered in 24 patients and the 5-year incidence of relapse for the entire group of patients was 42%. The 5-year leukemia-free survival for the: entire study patients, transplanted patients, and non-transplanted patients were: 43%, 38%, and 50% respectively. The 5-year overall survival for the: entire study patients, transplanted patients, and non-transplanted patients were: 44%, 34%, and 65% respectively. At the end of follow-up: 37 patients (59.68%) were alive, 24 patients (38.71%) were dead, and the fate of 1 patient (1.61%) was unknown as the patient moved to another hospital.

Conclusion: Administration of intensive consolidation chemotherapy for patients with AML at outpatient setting is safe, feasible, and cost-effective. The incidence of infectious complications was relatively low. No early treatment-related mortality due to intensive consolidation therapy was encountered. Outpatient administration of intensive consolidation therapy can save beds, reduce hospital costs, and is associated with short-term and long-term outcomes that are comparable to inpatient administration of consolidation therapy.

Introduction

AML, which arises from an uncontrolled proliferation of clonal hematopoietic stem cells, is defined by a broad spectrum of cytogenetic and molecular aberrations [1-5]. AML can be de novo or secondary to: Myelodysplastic Syndromes (MDSs), exposure to immunosuppressive, cytotoxic therapies, chemicals, and DNA-damaging agents [4,6]. The median age of diagnosis of AML is 68 years in the United States of America (USA) and the estimated 5-year Overall Survival (OS) is 24% - 30% [1,4,6]. According to the cytogenetic and molecular abnormalities, AML is classified into 3 risk categories: favorable, intermediate, and adverse risk [7-9]. Thorough evaluation of fitness to receive intensive chemotherapy should be performed once the diagnosis of AML is made [2,10]. Up to 45% of younger and 20% of older adults with AML can be cured with standard chemotherapy [11]. The induction chemotherapy with 7+3 regimen (cytarabine and idarubicin or daunorubicin) has remained the standard induction therapy in AML patients for > 40 years [2,4]. The current combinations of: gemtuzumab ozogamicin or midostaurin plus intensive chemotherapy; and azacitidine plus venetoclax represent the standards of care for AML patients who are fit or unfit for intensive chemotherapy respectively [2]. In August 2017, the Food and Drug Administration (FDA) in the USA approved the liposomal formulation of daunorubicin and cytarabine (CPX-351), for the treatment of adults with newly diagnosed secondary AML based on the results of a randomized phase III study which showed that CPX-351 had a significantly higher median OS than the standard 7+3 induction [12,13].

Younger AML patients can maintain longer Complete Remissions (CRs) with aggressive post-remission therapies including: allogeneic or autologous Hematopoietic Stem Cell Transplantation (HSCT), and intensive chemotherapy such as High-Dose (HD) cytarabine (HiDAC) [14]. HiDAC has been shown to be particularly effective in younger AML patients with favorable cytogenetics [15]. A meta-analysis that included 10 randomized phase III/IV trials compared benefit and safety of 3 dose regimens of cytarabine [HD: > 2-3 grams/meter squared (g/m^2)], intermediate-dose (ID): 1 - < 2 g/m^2, and low-dose (LD: < 1 g/m^2) showed that HiDAC in a dose of 3 g/m^2 twice daily for 3 days provided significant Disease-Free Survival (DFS) and anti-relapse effect [16]. In young adults with low-risk or intermediate-risk AML, repetitive cycles of HiDAC in a dose of 3 g/m^2 administered twice daily on days 1,3, and 5 has remained the standard consolidation therapy while a combination of post-remission therapies may be considered in High-Risk (HR) AML patients [17-19]. Two retrospective studies that compared ID cytarabine (IDAC) in a dose of 2 g/m^2 with HiDAC 3 g/m^2 both administered twice daily for 3 days as consolidation therapies for AML in adults showed comparable efficacy with no significant difference in the one-year Relapse Free Survival (RFS) and OS but less toxicity with IDAC thus making IDAC a more acceptable option for AML consolidation in adults [20,21]. However, a retrospective study showed that the three-year risk of relapse was significantly higher with IDAC compared with HiDAC. Consequently, HiDAC became the preferred regimen for single-agent cytarabine consolidation in young patients with favourable-risk AML [22]. Also, a systematic review that included 10 clinical studies and compared HD, ID and LD cytarabine given as consolidation treatment in AML patients with favorable cytogenetics showed that HD cytarabine provides a statistically significant RFS advantage over ID and LD cytarabine regimens [23].

Recently, there have been major advances in the management of AML that include: new insights on molecular pathogenesis, risk stratification, progress in genomics, use of Measurable Residual Disease (MRD), and introduction of several novel therapies [3,8]. In AML patients, achievement of MRD negativity is associated with superior DFS and OS while the presence of MRD prior to allogeneic HSCT is associated with increased relapse and worse survival [24,25]. In patients with AML, several mechanisms are responsible for drug resistance and relapse emerges from leukemic stem cells harbouring new genetic mutations [26,27]. Even in the presence of novel therapies, most patients with AML ultimately develop refractory/relapsed (R/R) disease [28]. New targeted therapies such as: menin inhibitors, isocitrate dehydrogenase (IDH1/2) inhibitors, FMS-Like Tyrosine kinase 3 (FLT3) inhibitors, CD33 inhibitors, bispecific antibodies, triple combinations that include hypomethylating agents plus B-cell leukemia/lymphoma-2 (BCL2) inhibitors, and enrolment in a clinical trial may bring hope for patients with R/R-AML [11,28,29]. In R/R-AML patients: (1) combinations of venetoclax and hypomethylating agents and/or intensive chemotherapy are well tolerated and can achieve high CRs to bridge responding patients to allogeneic HSCT, and (2) mutations in IDH1/2, Nucleophosmin-1 (NPM1), ASXL1, and chromatin-cohesin genes predict superior response, whereas mutations in FLT3-Internal Tandem Duplication (ITD) and K/N-RAS predict inferior response to venetoclax plus hypomethylating agents [27,29-34]. The cure rate of patients with R/R AML is < 10% and allogeneic HSCT is an option for only a minority of these patients [11]. A systematic review which included 24 studies in R/R-AMLs showed a median CR of 30% after salvage therapy, and a better survival of patients who received HSCT [35].

Allogeneic HSCT; which is indicated for primary refractory AML, relapsed disease, secondary AML, and AML with unfavorable genetics; has curative potential, is associated with HSCT-Related Mortality (HSCT-RM) and morbidity, and can prevent relapse in patients with AML in CR1 having adverse cytogenetics [5,36-40]. In AML patients, allogeneic HSCT can improve the OS, RFS, and DFS, while autologous HSCT is associated with significantly lower HSCT-RM but

higher relapse rate [5]. The recent advances in conditioning regimen, donor selection, Graft-Versus-Host Disease (GVHD) prophylaxis, and supportive care have broadened the eligibility for allogeneic HSCT, reduced rates of HSCT-RM, and improved outcomes [38,41-43]. Currently, treating de novo, secondary, therapy-related AML and R/R types of AML using haploidentical HSCT can achieve comparable outcomes to those of HSCT using: Matched Sibling Donor (MSD), Matched Unrelated Donor (MUD), or umbilical cord blood [39,40,42]. In AML patients having positive pre-transplantation MRD, haploidentical HSCT might be superior to MSD transplant in decreasing relapse and improving survival [42,43]. Allogeneic HSCT; from MSD, haploidentical donor or MUD; can offer prolonged survival and even cure in a significant proportion of patients with R/R AML [44]. Allogeneic HSCT is potentially curative for AML in adults ≥ 65 years old with medical comorbidities but it is associated with high HSCT-RM and non-relapse mortality [45-47]. Myeloablative conditioning (MAC) regimens have relatively high HSCT-RM in fit older patients with lower HSCT comorbidity index, but have lower risk of relapse [46]. Reduced Intensity Conditioning (RIC) and Non-Myeloablative (NMA) conditioning therapies have allowed allogeneic HSCT in older AML patients [45-47]. Post-transplant maintenance therapy and applications of cellular therapeutics are expected to overcome the remaining barriers to the success of HSCT including disease relapse [4].

Methods and materials

A retrospective study of patients with AML who received IDAC or HiDAC at outpatient setting between the 1st of August 2016 and the 31st of December 2023 at King Fahad Specialist Hospital in Dammam, Saudi Arabia was performed. The study was commenced in the year 2016 after ensuring safety of the study patients and full compliance with all hospital policies and guidelines. Strict inclusion and exclusion criteria for outpatient intensive consolidation chemotherapy were applied and vacant hospital beds were made available for those patients who require urgent admission due to any reason. Also, after having the needed explanations and health education, the patients included in the study gave informed consents to receive consolidation chemotherapy at outpatient setting. Subsequently, the medical records, and the clinical data as well as the laboratory data of all patients with AML who received outpatient consolidation therapy at our hospital during the time period specified above were retrieved for analysis.

During the study period, 4 patients with HR-Acute Promyelocytic Leukemia (APL) and 1 patient with myeloid sarcoma received outpatient consolidation therapy with IDAC or HiDAC. As per international protocols, patients with HR-APL usually receive induction therapy with All-Trans Retinoic Acid (ATRA) in addition to 3+7 regimen of chemotherapy then they receive 1-2 cycles of HiDAC consolidation chemotherapy. Also, patients with myeloid sarcoma should initially receive local radiotherapy followed by induction and consolidation cycles of chemotherapy, as per AML protocols, followed by allogeneic HSCT if they are transplant eligible.

In our study, HiDAC regimen of consolidation chemo therapy was composed of 2.5 - 3.0 g/m^2 of cytarabine given twice daily for 3 days, while IDAC regimen of consolidation chemotherapy was composed of cytarabine 1.0-2.0 g/m^2 administered twice daily for 3 days. Hyperleukocytosis was defined as white blood count (WBC) of > 100 x 10^9 /L. The grades of thrombocytopenia were defined as follows: mild thrombocytopenia: platelet (PLT) count of > 100 - 140 x 10^9 /L, moderate thrombocytopenia: PLT count of > 50 - 100 x 10^9 /L, severe thrombocytopenia: PLT count of 20 - 50 x 10^9 /L, while very severe thrombocytopenia: PLT count of < 20 x 10^9 /L. MRD evaluation was usually performed after achieving CR following induction or salvage chemotherapy and receiving the first cycle of consolidation chemotherapy.

After starting HiDAC or IDAC consolidation therapy, the study patients were commenced on prophylactic antimicrobials. Also, patients developing Febrile Neutropenia (FN) or infectious complications after receiving consolidation therapy were given daily granulocyte-colony stimulating factor (G-CSF) till neutrophil recovery. Early treatment-related mortality (TRM) was defined as death within the first 30 of receiving the consolidation cycle of chemotherapy. In recipients of HSCT, Primary Graft Failure (PGF) was defined as failure to achieve an absolute neutrophil count (ANC) of > 500 x 10^9 /L by 28 days post-HSCT.

Statistical analysis

The SSPS version 22 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Kaplan-Meier method with a log-rank test was used to estimate the survival rates and to identify risk factors that influenced the treatment outcome. OS was defined as the duration from the day of diagnosis until death or the date of the last follow-up for live patients with AML, APL or myeloid sarcoma. Leukemia Free Survival (LFS) was defined as the duration of survival from the day of diagnosis till the date of disease relapse or death due to any cause.

Results

During the study period of 7 years and 4 months, a total of 62 patients (57 with AML, 4 patients with APL, and 1 patient with myeloid sarcoma) received a total of 127 cycles of outpatient IDAC and HiDAC consolidation chemotherapy at our institution. Out of these 62 patients, there were 31 males and 31 females and their ages ranged between 15 and 63 years with a mean age of 37.4 years (Table 1). Out of the 57 patients with non-M3 AML, 49 patients had de novo AML while 8 patients had secondary AML [5 were secondary to MDSs, 1 was secondary to chronic myeloid leukemia, and

Table 1: Basic details of patients who received intermediate-dose or high-dose cytarabine consolidation therapy at outpatient setting.

Total Number of the Study Patients	62 patients
Gender	Males: 31; Females: 31
Age	Range: 15 - 63 years; Mean: 37.4 years
Primary Disease	Acute myeloid leukemia (AML): 57 patients
	High-risk acute promyelocytic leukemia (APL): 4 patients
	Myeloid sarcoma (MS): 1 patient
Clinical Presentation	Disease-related fever: 7 patients; Infections: 9 patients; Hepatosplenomegaly: 4 patients; Anemia ± bleeding: 23 patients; External lymphadenopathy: 3 patients; Weight loss: 4 patients; Leukostasis: 2 patients; Extramedullary disease (EMD) including MS: 12 patients; Incidental finding with no symptoms: 3 patients.
Laboratory Findings at Diagnosis	WBC count: > 100 x 10^9/L: 14 patients; 51 - 100 x 10^9/L: 8 patients; 11 - 50 x 10^9/L: 19 patients; ≤ 10 x 10^9/L: 21 patients
	Hb level: ≥ 10 g/dL:15; 7-10g/dL: 36; < 7 g/dL: 11
	PLT count: Normal: 5; 101 - 144 x 10^9/L: 7; 51 - 100 x10^9/L: 13; 21 - 50 x 10^9/L: 25; < 20 x 10^9/L: 12
Number of Patients Receiving Each Cycle of Consolidation Therapy	First: 60; Second: 41; Third: 23; Fourth: 3
Cytogenetics at Diagnosis	Favorable: 19 (30.65%); Intermediate: 24 (38.71%); Adverse: 17 (27.42%); Unknown: 2 (3.23%)
Relapses of Primary Disease	24 patients relapsed [15 relapses post-consolidation (62.5%); 9 relapses post-HSCT (37.5%)]
Patients who received HSCT	Total 36 patients: 29 in CR after induction; 6 in CR after salvage; 1 refractory [sequential transplant]
Fate at the End of the Study (Alive or Dead)	Alive: 37 (59.68%); Deceased: 24 (38.71%); Unknown: 1 (1.61%)

HSCT: Hematopoietic Stem Cell Transplantation; WBC: White Blood Cell; Hb: Hemoglobin; PLT: Platelet

2 were secondary to MDS/myeloproliferative neoplasms]. The subtypes of non-M3 AML were as follows: AML-M0: 8 patients; AML-M1: 3 patients; AML-M2: 18 patients; AML-M4: 7 patients; and AML-M5: 21 patients. The blood counts at presentation were very variable. Regarding the WBC counts: 14 patients (22.58%) presented with hyperleukocytosis; 8 patients (12.9%) had WBC of 51 - 100 x 10^9 /L; 19 patients (30.65%) had WBC of 11-50 x 10^9 /L; while 21 patients (33.87%) presented with WBC ≤ 10 x 10^9 /L. Regarding the hemoglobin (Hb) level: 15 patients (24.19%) presented with Hb ≥ 10 - 15 g/dL; 36 patients (58.06%) had Hb: 7 - 10 g/dL; and 11 patients (17.74%) had Hb: < 7 g/dL at diagnosis. Regarding the PLT counts at diagnosis: 5 patients (8.06%) had normal PLT count; 7 patients (11.29%) had mild thrombocytopenia; 13 patients (20.97%) had moderate thrombocytopenia; 25 patients (40.32%) had severe thrombocytopenia; while 12 patients (19.35%) had very severe thrombocytopenia (Table 1).

Clinically, the study patients had very variable manifestations at presentation. Nine patients (14.52%) presented with anemic manifestation alone; 7 patients (11.29%) had bleeding complications alone; 7 other patients (11.29%) had both manifestations of anemia and bleeding; 9 patients (14.51%) had disease-related fever; 9 patients (14.51%) presented with infectious complications; 4 patients (6.45%) had weight loss at diagnosis; 4 patients (6.45%) had hepatosplenomegaly at presentation; 3 patients (4.84%) presented with external palpable lymphadenopathy; and 12 patients (19.35%) presented with Extramedullary Disease (EMD) [3 skin, 2 nervous system, 3 gums, 1 pleura, 1 orbit, 1 mediastinum, and 1 kidney and peritoneum]. However, 3 patients (4.84%) were totally asymptomatic at presentation of their disease (Table 1).

Regarding the cytogenetic and molecular abnormalities at presentation were as follows: (1) 19 patients (30.65%) had favorable cytogenetic and molecular abnormalities: t 8,21: 4; t15,17: 4; inv 16: 2; RUNX1/RUNX1T1: 4; and mutated NPM1 without FLT3-ITD: 5; (2) 24 patients (38.71%) had intermediate-risk cytogenetic and molecular abnormalities: mutated NPM1 + FLT3-ITD: 18; t9,11 (MLL): 2; and normal cytogenetics in 4 patients; and (3) 17 patients (27.42%) had adverse cytogenetic and molecular abnormalities: monosomal karyotype: 4; complex cytogenetics: 4; trisomies and hyperdiploidy: 8; and t9,22: 1 patient. However, the cytogenetic and molecular abnormalities were unknown in 2 of the study patients (3.23%) (Table 1).

Cytoreductive therapy was required in 23 patients (37.1%) at presentation of their disease as they presented with WBC > 50 x 10^9/L. In 19 patients, hydroxyurea alone was used as cytoreductive treatment, leukapheresis plus hydroxyurea were used in 3 patients who presented with clinical manifestations of leukostasis, while cytarabine was used for cytoreduction in 1 patient. Induction chemotherapy consisted of: 3+7 regimen in 57 patients (91.94%); 2+5 regimen [2 doses of daunorubicin or idarubicin and 5 doses of cytarabone] in 1 patient; and 3+7 plus ATRA in the 4 HR-APL patients. Additional therapy was given in the form of sorafenib in 18 patients (29.03%) with FLT3-ITD mutation, and dasatinib in 1 patient (1.61%) with myeloid blast cell crisis of CML. Regarding the response to induction therapy: 57 patients (91.94%) achieved CR, 2 of them with incomplete hematological recovery while 5 patients (8.06%) were refractory to induction chemotherapy. The 5 patients with refractory disease were salvaged with: MEC (mitoxantrone, etoposide, and cytarabine) regimen in 4 patients and FLAG-IDA [fludarabine, cytarabine, idarubicin and G-CSF] in 1 patient. Four of these patients achieved CR after salvage therapy while 1 patient remained refractory to chemotherapy.

The first cycle of consolidation chemotherapy was given

to 60 patients (AML: 55, APL: 4, and myeloid sarcoma:1). Out of these patients: 57 were in first CR after 3+7 or 3+7+ATRA induction chemotherapy while 3 patients who were refractory to induction therapy and they received consolidation therapy after achieving CR following salvage chemotherapy. Among the 60 patients who received the first cycle of consolidation chemotherapy, 15 patients (25%) received HiDAC 3 g/m^2 twice daily for 3 days; 45 patients (75%) received IDAC [43 received 2 g/ m^2 and 2 received 1.5 g/m^2] twice daily for 3 days. No complications were encountered in 35 patients (58.33%). The following complications were encountered in the remaining patients: FN in 16 patients (26.67%), cytarabine fever in 2 patients; bacteremia in 1 patient, Invasive Fungal Infections (IFIs) in 2 patients, and arrhythmias and heart failure in 2 patients. Twenty patients (33.33%) required hospital admission, none of them needed intensive care unit (ICU), and no early TRM was encountered. MRD evaluation was performed after the first cycle of consolidation and the results were as follows: 36 patients (60%) had negative MRD, and 14 patients (23.33%) had positive MRD. However, MRD was not done for 10 patients (16.67%) due to different reasons, mainly the restrictions during the COVID-19 pandemic. For patients who had positive MRD, they were planned to receive either HiDAC as next cycle of consolidation or a total of 4 cycles of IDAC consolidation chemotherapy (Table 2).

The second cycle of consolidation chemotherapy was given to 41 patients. Among these patients, 10 patients (24.39%) received HiDAC 3 g/m^2 twice daily for 3 days; and 31 patients (75.61%) received IDAC [28 received 2 g/ m^2 and 3 received 1.5 g/m^2] twice daily for 3 days. No complications were encountered in 28 patients (68.29%). The following complications were encountered in the remaining patients: FN in 13 patients (31.71%), bacteremia in 2 patients, IFIs in 2 patients, drug-related fever in 1 patient. Eighteen patients (43.90%) required hospital admission, none of them needed ICU care, and no early TRM was encountered (Table 2). The third cycle of consolidation chemotherapy was given to 23 patients. Among these patients, 5 patients (21.74%) received HiDAC 3 g/m^2 twice daily for 3 days; and 18 patients (78.26%) received IDAC [15 received 2 g/ m^2 and 3 received 1.5 g/m^2] twice daily for 3 days. No complications were encountered in 13 patients (56.52%). The following complications were encountered in the other patients: FN in 9 patients (39.13%), and bacteremia in 2 patients. No IFIs or drug-related fever were encountered. Eight patients (34.78%) required hospital admission, none of them needed ICU care, and no early TRM was encountered (Table 2). The fourth cycle of consolidation chemotherapy was given to 3 patients, all of them received IDAC [2 received 2 g/m^2 and 1 received 1.5 g/m^2] twice daily for 3 days. No complications were encountered in the 3 patients, no hospital admissions were required, and no early TRM was encountered (Table 2).

For the 62 study patients who received a total of 127 cycles of HiDAC and IDAC consolidation therapy, the overall results were as follows: the median times for recovery of ANC (> 0.5 x 10^9/L) and PLTs (> 20 x 10^9 /L) were 21 days (range: 17 - 24) and 23 days (range: 18 - 26) respectively; FN developed in 38 cycles (29.92%) of chemotherapy; documented bacterial and IFIs developed in 8 cycles (6.3%) of chemotherapy; hospital admissions were needed following 46 cycles (36,22%) of consolidation therapy; the duration of hospitalization ranged between 2 and 7 days with a mean of 5 days; no complications were encountered following 79 cycles (62.2%) of chemotherapy; and no early TRM was reported following the cycles of consolidation therapy administered [Table 2].

Out the 62 patients studied, 36 patients (58.06%) received HSCT: 29 of these patients (80.56%) received HSCTs (28 allogeneic and 1 autologous) after achieving CR following induction therapy, 6 patients (16.67%) received their allografts after achieving CR following salvage therapy for R/R-AML, while 1 patient (2.78%) with AML received sequential allogeneic transplantation while having disease refractory to salvage therapy. The patient who received

Table 2: Details of the Cycles of HiDAC and IDAC Consolidation Therapy Administered at Outpatient Setting for the Study Patients.

Specific Consolidation Cycles	Number of Patients in Each Cycle of Consolidation Therapy		Febrile Neutropenia		Hospital Admissions		Documented Bacteremial and Invasive Fungal Infections (IFIs)		No Complications Encountered	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
First Cycle of Consolidation	60	47.24%	16	26.67%	20	33.33%	Bacteremia: 1 IFIs: 2	Bacteremia: 1.67% IFIs: 3.33%	35	58.33%
Second Cycle of Consolidation	41	32.28%	13	31,71%	18	43.90%	Bacteremia: 2 IFIs: 2	Bacteremia: 4.88% IFIs: 4.88%	28	68.29%
Third Cycle of Consolidation	23	18.11	9	39.13%	8 [1 to ICU]	34.78%	Bacteremia: 1 IFIs: 0	Bacteremia: 4.35% IFIs: 0.0%	13	56.52%
Fourth Cycle of Consolidation	3	2.36	0	0.0%	0.0	0.0%	Bacteremia: 0 Fungal: 0	Bacteremia: 0.0% IFIs: 0.0%	3	100%
Total	127	100%	38	29.92%	46	36.22%	Bacteremia: 4 IFIs: 4	Bacteremia: 3.15% IFIs: 3.15%	79	62.20%

HiDAC: High-Dose Cytarabine; IDAC: Intermediate-Dose Cytarabine; ICU: Intensive Care Unit

autologous HSCT for HR-AML had already refused to have an allogeneic HSCT. The indications of HSCT were: AML with HR cytogenetics in 17 patients (47.22%); AML with EMD (11 patients) or myeloid sarcoma (1 patient) in 12 patients (33.33%); and R/R AML in 7 patients (19.44%) (Tables 1 and 3). The forms of allogeneic HSCT were as follows: 31 patients (86.11%) received MSD-HSCT, 3 patients (8.33%) receive haploidentical allografts, while 1 patient (2.78%) received MUD allograft. The pre-transplant conditioning therapies were: MAC in 33 patients (91.67%) while RIC or NMA were given to 3 patients (8.33%). Acute GVHD developed in 9 patients (25%): skin in 4, skin and Gastrointestinal Tract (GIT) in 2, skin + GIT + liver in 1, and GIT alone in 2 patients. Chronic GVHD, mostly involving multiple organs, was encountered in 14 patients (38.89%): skin in 7, liver in 8, lung with bronchiolitis obliterans picture in 5, pericardium with pericardial effusion in 1, mouth and upper GIT in 9, and eyes and nails in 3 patients. In the early post-HSCT period: FN was encountered in 8 patients, 2 of these were complicated by bacteremia; grades II-III mucositis in 2 patients; hemorrhagic cystitis in 3 patients; veno-occlusive disease of liver in 1; thrombotic microangiopathy in 2 patients, and PGF in 1 patient. Other complications that evolved at later stages during the transplantation course included: 13 documented bacterial infections [8 had septic episodes] including 2 episodes of colitis due to Clostridium difficile, 8 viral infections [5 with cytomegalovirus, 2 with Epstein-Barr virus, and 1 with varicella zoster virus], 5 IFIs [4 with Aspergillus species, and 1 with Fusarium species], and 1 infection with Pneumocystis jiroveci pneumonia. Arrhythmias were encountered in 2 patients, severe GIT bleeding in 1 patient, and 1 leukostasis due to aggressive relapse post-HSCT. At the end of follow-up, 22 HSCT recipients (61.11%) were alive and 14 transplant recipients (38.89%) were dead. The causes of death were: PGF in 1; relapses or progressive disease in 8, and steroid-refractory GVHD and its immunosuppressive therapy in 5 patients. However, 12 of the deceased patients had bacteremia and septic shock (Table 3).

Disease relapses were encountered in 24 of the study patients (38.71%), 15 of these disease relapses (62.5%) were encountered in recipients of HSCT while relapses occurred in 9 patients (37.5%) following IDAC and HiDAC consolidation cycles of chemotherapy (Table 1). At the time of diagnosis, 7 relapsed patients (29.17%) had adverse cytogenetics, 10 had intermediate-risk (41.67%), while 7 patients (29.17%) had favorable cytogenetic profiles. At the time of relapse, 6 of the relapsed patients acquired new cytogenetic and molecular abnormalities. At the end of follow-up, 4 of the relapsed patients (16.67%) were alive, while 20 of the relapsed patients (83.33%) died subsequently due to various reasons including: progressive disease with organ involvement and leukostasis in 9 patients and infectious complications including sepsis in 7 patients. In the recipients of HSCT, disease relapses occurred at a mean of 24.72 months post-HSCT while in the non-transplant group of patients, relapses were encountered at a mean of 6.25 months after the last cycle of consolidation therapy. The 5-year incidence of relapse for the entire population of patients was 42% (Figure 1).

Regarding the fate of the entire study population at the end of follow-up: 37 patients (59.68%) were alive, 24 patients (38.71%) were dead, and the fate of 1 patient (1.61%) was unknown as the patient moved to another hospital (Table1). The median LFS for: the entire study patients, the patients who received HSCT, and the patients not subjected to HSCT were: 35.6 months; 35.6 months; and 16 months respectively. The 5-year LFS for: the entire study patients, the transplanted patients and the non-transplanted patients were: 43%; 38%; and 50% respectively (Figure 2). The median OS for: the entire study patients, the transplanted patients, and the non-transplanted patients were: 61.6 months; 51 months; and 94.6 months respectively. The 5-year OS for the: entire study patients, transplanted patients and non-transplanted patients were: 44%; 34%; and 65% respectively (Figure 3).

Table 3: Details of the patients with acute myeloid leukemia (AML) or myeloid sarcoma who received hematopoietic stem cell transplantation (HSCT).

Disease and HSCT Features	Details	More Details and Percentages
Indications for HSCT	AML with high-risk (HR) cytogenetics: 17 AML with extramedullary disease (EMD) or myeloid sarcoma (MS): 12 Relapsed/Refractory (R/R) AML: 7	AML with HR cytogenetics: 47.22% AML with EMD or MS: 33.33% R/R-AML: 19.44%
Type of HSCT	Autologous HSCT: 1 Matched sibling donor (MSD) allogeneic HSCT: 31 Haploidentical HSCT: 3 Matched unrelated donor (MUD): 1	Autologous HSCT: 2.78 MSD allogeneic HSCT: 86.11% Haploidentical HSCT: 8.33% MUD allogeneic HSCT: 2.78%
Conditioning Therapy	Myeloablative conditioning (MAC): 33 Non-myeloablative (NMA) and reduced intensity conditioning (RIC): 3	MAC: 91.67% NMA and RIC: 8.33%
Disease Status Before HSCT	Complete remission (CR) achieved after induction therapy: 29 CR achieved after salvage chemotherapy: 6 Refractory disease: 1	CR after induction: 80. CR after salvage therapy: 16.67% Refractory disease: 2.78%
Post-HSCT Complications	Acute graft versus host disease (GVHD): 9 Chronic GVHD: 14 Mucositis; grades: II to III: 2 Hemorrhagic cystitis: 3 Vono-occlusive disease of the liver: 1 Primary graft failure: 1 Early and late documented infections: 27	Acute GVHD: 25% Chronic GVHD: 38.89% Infections: Bacterial: 13 (36.11%) Viral: 8 (22.22%) Fungal: 5 (13.89%) Pneumocystis jiroveci pneumonia: 1 (2.78%)
Outcome at End of Follow-Up	Alive: 22 Deceased: 14	Alive: 61.11%; Deceased: 38.89% Causes of death: Graft failure: 1 (7.14%) Relapse or disease progression: 8 (57.14%) GVHD complications and infections: 5 (35.71%)

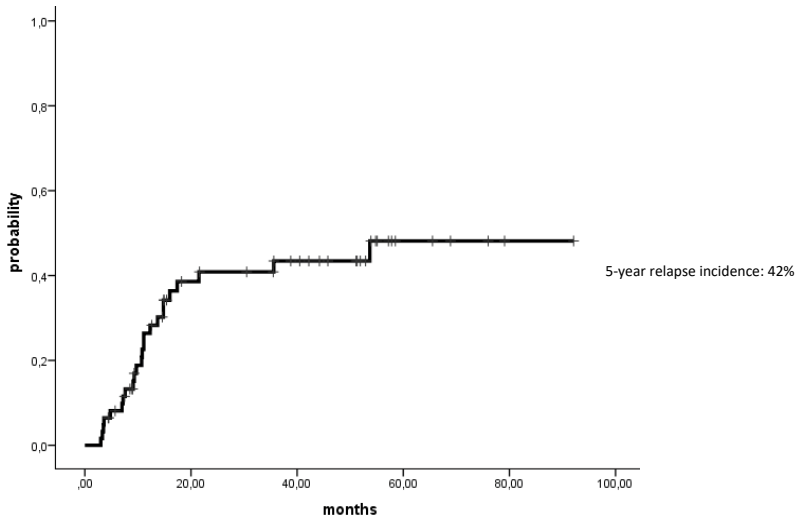

Figure 1: Relapse Incidence After Consolidation with High-Dose and Intermediate–Dose Cytarabine Given at Outpatient.

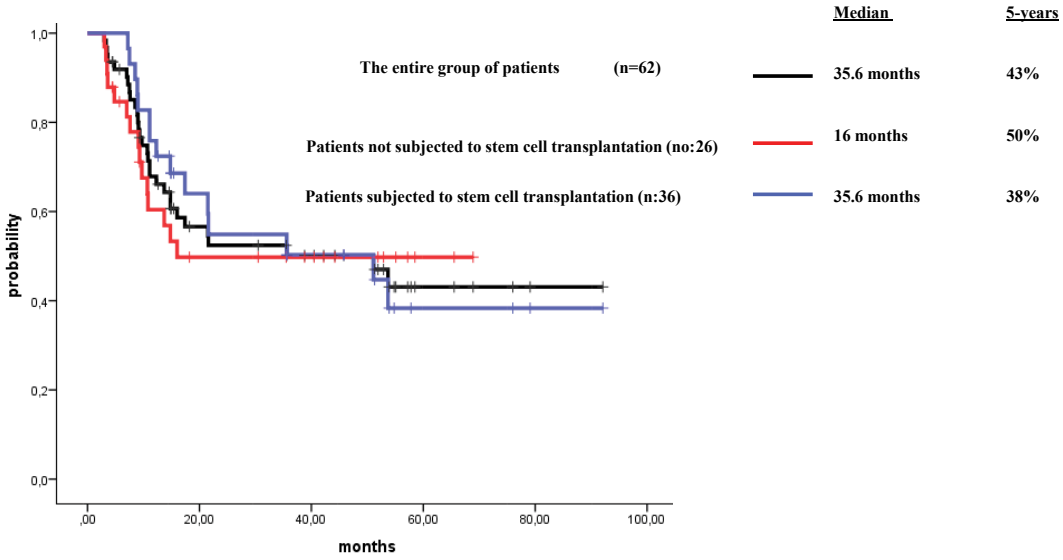

Figure 2: Leukemia Free Survival after Outpatient Consolidation with High-dose and Intermediate-Dose Cytarabine.

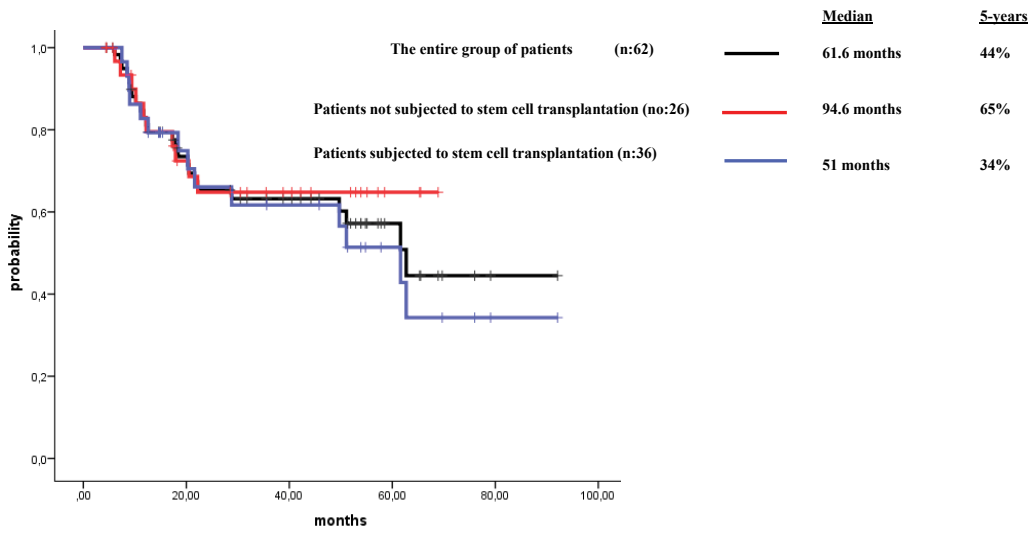

Figure 3: Overall Survival after Consolidation with High-Dose and Intermediate-Dose Cytarabine Administered at Outpatient.

Discussion

In adult patients with AML, intensive chemotherapeutic regimens with curative intent, such as induction and consolidation, are followed by prolonged periods of profound pancytopenia during which the following complications may be encountered: side effects of the administered chemotherapeutic agents, frequent need for transfusion of blood products, and HR of hospital-acquired infections some of which may need ICU admission. Consequently, these patients have traditionally been hospitalised for the duration of chemotherapy and until blood count recovery [48-52]. However, the care of patients with hematologic malignancies treated with intensive therapeutic modalities is increasingly shifting from inpatient to outpatient settings due to the improved capabilities to provide supportive care, monitor patients regularly, and expedite admission to hospital when necesary which have facilitated this change in practice [48,49,51,52]. Several studies have shown that, in selected patients with AML, intensive induction and consolidation chemotherapy can be administered either entirely as outpatient or alternatively they can be given as inpatient followed by early hospital discharge as both strategies have been proven to be safe, feasible, well tolerated and cost-effective [50-54]. Advantages of outpatient management of AML include: (1) significant reductions in the utilization of medical resources and in healthcare costs, (2) improvement in quality of life (QoL), and (3) decreased rate of septicemia and hospital-acquired infections [49,52,55]. Effective implementation of an outpatient intensive chemotherapy program requires: (1) proper infrastructure, (2) multidisciplinary team-based approach that includes nurses, social works, medical providers, and pharmacists and (3) careful planning in order to provide the necessary support, education and rapid management of serious complications that occur among this very vulnerable patient population. However, barriers and challenges to the successful implementation of outpatient care models in AML patients include: (1) limited outpatient infrastructure, (2) geographical limitations; (3) lack of careful planning to provide the necessary support and education; and (4) rapid management of serious complications that evolve among this vulnerable patient population [49,51,54]. Once the vital requirements of outpatient care for patients with hematologic malignancies are available, not only outpatient intensive chemotherapy, but also various forms of HSCT can safely be given at outpatient setting [50,52,54,56-58]. After ensuring the availability of the following requirements: proper hospital infrastructure, active multidisciplinary team, education of patients and health providers, and having all the needed plans including the strict inclusion and exclusion criteria, our outpatient program for administration of HD chemotherapy such as intensive consolidation therapy for AML patients was initiated in the year 2016.

Several studies have shown safety, feasibility, and cost-effectiveness of outpatient administration of IDAC: 1.5 - 2.0 g/m^2 twice daily for 3 days; administered on days:1,3, and 5 or days: 1-3 as well as HiDAC: 3 g/m^2 twice daily for 3 days; given on days:1,3, and 5 or days: 1-3 as consolidation chemotherapy in the management of selected adult patients with AML in remission [59-70]. Eligibility criteria for outpatient administration of HiDAC or IDAC consolidation chemotherapy include: (1) age ≥ 14 years; (2) absence of active, residual, or severe preceding infection; (3) good performance status with normal chest x-ray and biochemistry; (4) having CR after one cycle of 7+3 induction; (5) timely reach of the hospital services and residence within 1-3 hours distance from the treatment center; (6) availability of local housing and/or a caregiver support; (7) support of trained nursing staff; (8) having enough infusion room capacity; (9) receiving prophylactic antimicrobials; (10) insurance coverage for outpatient cytarabine; and (11) good compliance record and participation in regular and close follow-up [60,63,69]. Exclusion criteria of outpatient HiDAC include: (1) lack of caregiver, (2) poor performance status, and (3) organ dysfunction [59,62]. In our study, the inclusion criteria for HIDAC or IDAC consolidation therapy at outpatient setting were: (1) good performance status; (2) absence of active infection; (3) absence of organ dysfunction or failure (4) absence of uncontrolled comorbid medical condition; (5) achieving CR after induction or salvage chemotherapy; (5) residence within 1 hour distance from the hospital; (6) availability of a caregiver (7) receiving prophylactic antimicrobials; and (8) good compliance record of the patient. Our exclusion criteria included: (1) lack of caregiver, (2) poor performance status, (3) active infection or uncontrolled comorbid medical condition, (4) organ dysfunction or failure, and (5) history of poor compliance.

Advantages of outpatient administration of cytarabine: (1) saving beds and reducing hospital stay, (2) reduced hospital costs, (3) reduced risk of hospital-acquired infections, (4) reduced the rate of delay between the cycles of chemotherapy, and (5) improved patient satisfaction, QoL, and psychosocial well-being of patients [49,60-62,64,66]. Disadvantages and complications of outpatient HiDAC and IDAC include: cytarabine-related reactions including: fever, skin eruptions, and neurotoxicity; mucosal bleeding; vomiting; FN; as well as bacteremia and septic shock requiring hospital admission [59-62,64,66]. However, complications of chemotherapy and non-relapse mortality were more frequently encountered in AML patients older than 50 years [66]. In our study, the main advantages of outpatient HiDAC or IDAC were: saving beds, decreasing hospital costs, reducing the rate of hospital-acquired infections and absence of early TRM.

The reported median times for recovery of ANC and PLT count after receiving HiDAC or IDAC at outpatient were 12 - 25 days and 19 - 32 days respectively [55,60,62,68]. Studies reported that bacteremia developed following 13.0% to 31.3% of the cycles of HiDAC and IDAC administered at outpatient

setting [55,61,66]. Several studies reported that the incidence of hospitalization after HiDAC or IDAC consolidation chemotherapy at outpatient setting ranged between 18.75% and 47.4% [59,60,63,64,66,67,69,71]. The reported length of hospital admission following HiDAC chemotherapy ranged between 4.3 days and 11 days [60,61,64]. The reported incidence of early TRM after receiving HiDAC or IDAC consolidation at outpatient was very variable and it ranged between 0.0% and 18.51% [55,60-62,66,68,70]. The rates of FN, bacteremia, ICU admission, and death were significantly higher during the second consolidation, as compared with the first, in both younger and older patients [70]. The reported disease relapses occurred in 30.3% - 64.0% of AML patients who received HiDAC or IDAC at outpatient setting [55,63,66,69]. The proportion of AML patients who received HiDAC or IDAC at outpatient setting and subsequently underwent allogeneic HSCT in CR1/CR2 ranged between 9.5% and 37.1% [55,61,63]. One study reported that the 2-year OS rates of AML patients receiving outpatient HiDAC and IDAC were 57.1% and 83.3% respectively, while the 2-year RFS rates were 57.1% for HDAC-16 and 66.7% for IDAC respectively [65]. However, another study reported 2 years OS for patients receiving HiDAC at outpatient setting to be as low as 23% [63]. With proper patient selection, dosing, and education of both health providers and patients, HiDAC and IDAC can be safely administered in the outpatient setting and may even become the standard of care without compromising the on-time delivery of chemotherapy or clinical outcome in certain institutions [59,69]. For our 62 study patients who received a total of 127 cycles of HiDAC and IDAC consolidation therapy at outpatient: the median times for recovery of ANC (> 0.5 x 10^9 /L) and PLTs (> 20 x 10^9/L) were 21 days and 23 days respectively; FN developed in 29.92% of the cycles of chemotherapy; documented bacterial and IFIs developed following 6.3% cycles of chemotherapy; hospital admissions were needed following 36.22% cycles of consolidation therapy; the mean duration of hospitalization was 5 days; no complications were reported following 62.2% cycles of chemotherapy; and no early TRM was encountered following all the cycles of consolidation therapy. Additionally, HSCT was performed in 58.06% of patients, and relapses occurred in 38.71% patients. At the end of follow-up, 59.68% of patients were alive and 38.78% were dead. The 5-year relapse incidence of the entire study patients was 42%. The 5-year LFS for the: entire study patients, recipients of HSCT, and patients not subjected to HSCT were: 43%, 38%, and 50% respectively. The 5- year OS for the: entire study patients, recipients of HSCT, and non-transplanted patients were: 44%, 34%, and 65% respectively. The relatively worse 5-year LFS, and OS for patients subjected to HSCT compared to non-transplanted patients can be explained by the following: (1) the transplanted group of patients had HR features such as adverse cytogenetics and EMD at diagnosis; (2) several patients with R/R-AML had HSCT after control of their diseases; and (3) encountering more frequent and more serious infectious complications such as bacteremia and septic shock in the recipients of HSCT due to their profound immunosuppression. Nevertheless, the 5-year OS, LFS, and incidence of relapse for the: entire population of patients, transplanted and non-transplanted patients were similar to long-term outcomes reported by other studies in AML patients.

Several retrospective and prospective studies have shown that, for selected AML patients, administration of intensive consolidation chemotherapy as inpatient then early hospital discharge followed by outpatient management is feasible, safe, well tolerated, cost-effective, and may reduce the incidence of infections with drug resistant hospital-acquired pathogens [50,53,72,73]. Inclusion criteria for early discharge and outpatient management of AML patients include: (1) absence of fever, (2) use of appropriate prophylactic or therapeutic antimicrobials, (3) clinical and hemodynamic stability, (4) availability of a caregiver and an accommodation within 60 min of the center, and (6) absence of serious co-morbidities [72-74]. Exclusion criteria for early discharge after intensive chemotherapy include: (1) sepsis, (2) serious medical complications, and (3) social and geographic factors [48,73,74]. Early discharge following intensive AML chemotherapy is associated with lower rates of: hospital admission, days of hospitalization, hospital costs, infectious complications, use of intravenous antibiotics, and TRM [48,53,74]. Our study included patients who received intensive consolidation chemotherapy at outpatient setting, but none of the patients who had consolidation therapy as inpatient followed by early discharge were included.

Despite including a relatively large number of patients in our study and that the study extended over 7 years and 4 months, we acknowledge that retrospective studies have their own limitations.

Conclusion and recommendations

In patients with AML, outpatient administration of IDAC and HiDAC consolidation chemotherapy is safe, feasible and cost-effective provided enough preparations are made, the hospital infrastructure allows, specific inclusion and exclusion criteria are applied, and instructions are strictly followed. In our study, the main advantages of outpatient administration of intensive consolidation chemotherapy were: saving beds; reducing hospital costs; decreasing infectious complications; improvement of patient satisfaction, QoL, and psychosocial well-being of patients; and decreasing early TRM to 0.0%.

Authors' contributions

All authors participated in the management of the patients included in the study. Also, all authors read and approved the final form of the manuscript.

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