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INVASIVE FUNGAL INFECTIONS IN ADULT PATIENTS WITH ACUTE LEUKEMIA: A 2-YEAR PROSPECTIVE OBSERVATIONAL STUDY AT A TERTIARY CARE CANCER CENTRE IN SOUTH INDIA.

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ABSTRACT

Objectives: Invasive fungal infections (IFIs) are important causes of treatment failure and death in acute leukemia. Candida and Aspergillus are the common pathogens. Conventional amphotericin-B deoxycholate (AmB) has been the mainstay of treatment. Newer formulations such as liposomal amphotericin-B (LAmB), amphotericin-B lipid complex, echinocandins and triazoles are less toxic and have a broader spectrum of activity.

Our aim was to study the spectrum of IFIs in adults with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) and efficacy and safety of firstline AmB.

Materials and methods: This single centre, prospective, observational study conducted over two years (2013- 2015) had 123 adults (58 with ALL and 65 with AML).

Results: Out of 178 courses of chemotherapy administered during the study period, 98 (55%) of all-category IFIs were identified. 26.4% (47/178) were during induction therapy for AML.As invasive interventions were withheld due to severe thrombocytopenia and neutropenia, majority of IFIs were classified as possible (30.9%), most common sites were bloodstream and lung. There was one probable (pulmonary aspergillosis) and three proven IFIs (candidemia-2 and T.asahii - 1). IFIs were an important cause of induction mortality (40% in ALL and AML). Baseline neutropenia, relapsed-refractory diseases were important pre-treatment risk factors associated with the incidence of IFIs. Prolonged and severe neutropenia was an important post-treatment risk factor. AmB was the firstline antifungal agent used in 96 episodes. Only 9 patients switched over to 2nd line agents (voriconazole -5 and caspofungin- 4). The most common adverse effect of AmB was hypokalemia (CTCAE Grade1 and 3) (6.9%) followed by infusion-related reactions (Grade 2) (34.4%) and reversible renal impairment (Grade 2) (2.1%).

Conclusion: IFIs are important causes of morbidity and mortality in acute leukemia especially during intensive induction therapy and in relapsed-refractory disease. AmB is a reasonable firstline agent with manageable toxicities. Use of 2nd line antifungals on the basis of pre- and post-treatment risk factors will improve outcomes.

KEYWORDS : .Invasive fungal infections, acute lymphoblastic leukemia, acute myeloid leukemia, conventional amphotericin-B deoxycholate

Introduction:

Invasive fungal infections (IFIs) are important causes of morbidity and mortality in neutropenic patients with hematological malignancies (HM). Conventional amphotericin-B deoxycholate (AmB) is the cornerstone of therapy but is associated with significant toxicity [1,2,3]. Newer formulations of amphotericin-B, triazoles and echinocandins have favorable toxicity profiles and have a broad spectrum of activity [4].

Our aim was to study the spectrum of IFIs in adults with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) and the efficacy and safety of firstline AmB.

Materials and methods:

This prospective observational study was conducted at a tertiary cancer centre, from October 1st, 2013 to September 30th, 2015. We enrolled newly diagnosed patients with ALL, including lymphoblastic lymphoma and AML, including AML-M3 who received chemotherapy (BFM-95 protocol, HyperCVAD, 3+7 induction, HDAC, FLAG-IDA, ATO+ATRA, LDAC, decitabine) during this period. Data was collected from patient files and electronic records.

Firstline treatment of B-ALL and T-ALL was as per the BFM-95 protocol. Relapsed ALL was treated with hyperCVAD alternating with HDMTX and cytarabine. Induction therapy for non-M3-AML in patients <60 years was 3+7 (daunomycin 60 mg/m2 for three days and cytarabine 100mg/m2 intravenous (IV) infusion over 24 hours for seven days). Allogeneic stem cell transplant (allo-SCT) is not performed in our institute. Patients eligible for allo-SCT were referred elsewhere if willing. Favorable risk patients and those not willing for allo-SCT received consolidation with four cycles of HDAC (3g/m2 twice daily for three days). Relapses were treated with FLAG-IDA. Patients ≥60 years received LDAC (10 mg/m2/day subcutaneously for 7-10 days, every four weeks) or decitabine (20 mg/m2/day, IV for five days, every four weeks). Routine prophylactic G-CSF was used after HDAC, FLAG-IDA and hyperCVAD.

Treatment response was defined according to ELN guidelines [5, 6]. We defined induction mortality as all-cause-mortality from day1 of induction chemotherapy until the recovery of counts or till the next cycle. Mortality attributable to IFI was defined as death with persistent symptoms and/or signs of IFI.

Patients received prophylactic antimicrobials during induction phase A and B of BFM-95, FLAG-IDA, 3+7 induction and hyperCVAD. Antifungal prophylaxis was oral fluconazole 200 mg daily. For probable/proven IFIs we suggested secondary prophylaxis with posaconazole or voriconazole which most of our patients couldn't afford and chose to continue fluconazole. Induction chemotherapy was given in general/special ward/ leukemia wards or intensive care unit (ICU) based upon the patients' general condition and availability of beds. ICU was fumigated every three months. None of the wards had HEPA-filter. Surveillance cultures were not practiced.

By day 4, if fever persisted despite adequate systemic antibiotics, AmB was added. It was started earlier in patients with rapid deterioration prior to this point. The other indications were persistent fever despite 48 hours of secondline antibiotics, bronchopneumonia, extensive candidiasis involving mouth and oropharynx, sinonasal infection. Adverse events (AEs) were graded according to common terminology criteria for adverse events [7].

Biphasic media were used for blood culture viz. Brain Heart Infusion and Mac Conkey's media, Sabouraud's Dextrose broth and thioglycollate broth within the 1st hour of the febrile episode. Chest x-ray (CXR) and sputum culture were done in case of lower respiratory tract infection (LRTI). Bronchoalveolar lavage (BAL), fine needle aspiration cytology (FNAC) and biopsy were not done. High resolution computed tomography of the chest was withheld as the poor general condition of our patients forbade us from shifting them for the procedure. Serum Aspergillus galactomannan index (s-GMI) was unavailable in our institution at that time.

IFIs were diagnosed according to the EORTC/MSG 2008 guidelines [8]. Suspected IFI was defined as fever >38°C persisting for > 96 hours of IV antibiotics without positive blood culture [9]. We diagnosed

fungal pneumonia in those with consolidation/cavity/fungal balls on CXR, negative Ziehl-Neilson stain for acid-fast bacilli and clinical/radiological response to antifungals, with/without positive sputum cultures. Skin involvement- erythematous maculopapular, pustular lesions, black eschar and spreading cellulitis responding to antifungals; involvement of nose, paranasal sinuses, orbit - serosanguineous nasal discharge, black eschar or cellulitis on the skin overlying the sinuses, proptosis and conjunctival suffusion, sinus tenderness responding to antifungals were considered as IFIs.

Statistical analysis:

Patients were stratified based on the presence of baseline neutropenia, disease status (newly diagnosed vs. relapsed-refractory), risk group (high risk vs. low and intermediate risk), age, duration and severity of neutropenia and oral mucositis. The data was expressed in percentages. Data was analyzed using GraphPad QuickCalcs software (www.graphpad.com) and evaluated by a 2 x 2 contingency table employing Fisher's Exact Test. $p<0.05$ was statistically significant.

Results:

There were 123 adults - 58 with newly diagnosed ALL and 65 with AML. Their demographic characteristics are shown in Table 1. The median age was 20 years (range, 15-56 years), with a male-to-female ratio of 1.6:1 for ALL, for AML the median age was 29 years (range, 15-72 years) and the male-to-female ratio was 1.52:1. They were stratified as standard/good (0%), intermediate (81%) and high (19%) risk as per the guidelines in the BFM-95 protocol for ALL, and favorable (32.3 %), intermediate(52.3%) and high (15.4%) risk as per cytogenetics for AML (FLT3-ITD/NPM1/CEBPA mutation analysis were not done in everyone due to financial constraints).

Outcomes of induction therapy are shown in Table 2. At the end of ALL induction, 49 (84.5%) achieved complete remission (CR), 4 (6.9 %) had refractory disease and 5 (8.6%) died. At the end of AML induction therapy, 43 (66.2 %) achieved CR, 2 (3.1 %) had refractory disease and 20 (30.7 %) died.

In the 178 courses of chemotherapy administered during the study period, 98 (55 %) of all-category IFIs were identified, including 39 (21.9 %) suspected, 55 (30.9 %) possible, 1(0.6 %) probable and 3 (1.6 %) proven. Majority occurred during 3+7 induction (26.4%, 47/178) followed by induction therapy for ALL (15.2%, 27/178), HDAC (7.9%, 14/178) and others (5.1%, 9/178) (FLAG-IDA-1, ATRA+ATO induction-2, decitabine-2, consolidation with HDMTX-1, reinduction therapy-1)

Of the proven IFI, there were two episodes of candidemia, one in a patient receiving AML induction and another in a patient with relapsed ALL receiving second cycle of HyperCVAD. One patient receiving AML induction developed Trichosporon asahii fungemia. All these survived. There was one case of pulmonary aspergillosis (probable IFI) during AML induction; CXR revealed multiple fungal balls and sputum culture grew Aspergillus. This patient died due to extensive pulmonary involvement. Of the 55 patients with possible IFI, 27 had radiological signs highly suggestive of IA – 18 with CXR showing bronchopneumonia, 5 with multiple cavities and 4 had sinusitis evident on x-ray of the paranasal sinuses.

The infection sites attributable to all categories of IFI were analyzed. Of the 109 sites of infection identified in 98 episodes of IFI, majority were bloodstream infections (48.6%, 53/109), followed by pneumonia (22%, 24/109), involvement of the digestive tract (22%, 24/109), sinonasal involvement (3.7%, 4/109) and skin (3.7%, 4/109).

Initial empirical antifungal therapy with AmB was used in 96 episodes of IFI. Two received firstline caspofungin due to renal failure. Switchover to voriconazole and caspofungin was done in 5 and 4 episodes respectively. Two each received secondary prophylaxis with voriconazole and posaconazole. The median duration of antifungal use was 12 days (range, 3-51 days).

The most common AE of AmB was hypokalemia, seen in 46.9% (46/98). The median potassium level while on treatment was 3.5 mEq/L (Range, 1.8-5.1mEq/L). All patients responded to potassium supplementation. There were 33 (34.4%) episodes of infusion-related reactions (IRRs).There were 2 (2.1%) episodes of renal impairment attributable to AmB. These patients were switched over to caspofungin. Grading of AEs of AmB is shown in Table 3. There were no AEs associated with voriconazole or caspofungin.

The correlation between the incidence of IFIs and pre and post-treatment risk factors is illustrated in Table 4. Presence of baseline neutropenia (ANC <500/mm3 at the time of diagnosis), relapsed-refractory leukemia and prolonged and severe neutropenia (ANC <100/mm3 for >10 days) correlated with the incidence of IFIs. Interestingly, presence of high risk acute leukemia (ALL and AML), age ≥60 years, presence of central line and oral mucositis (≥ Grade 3) did not correlate significantly.

During the study period, 32.3% (21/65) patients with AML died. Nine of these were attributable to IFIs, accounting for 42.9% (9/21). There were 12.1% deaths (7/58) among patients with ALL. Two out of these were attributable to IFIs, accounting for 28.6% (2/7). The induction mortality for AML and ALL was 30.7% (20/65) and 8.6% (5/58), IFIs accounted for 40% of the early deaths in AML (8/20) and ALL (2/5). None of the deaths were attributable to the AEs of antifungals.

Discussion:

Ours is a tertiary cancer centre located in the state capital. We treat patients from the rest of India as well. We cater mainly to patients from a low socioeconomic status. Most of the chemotherapeutic agents and some of the anti-microbials (AmB and fluconazole which are relevant to this article) and investigations are funded by a state sponsored scheme. We utilize resources judiciously so as to diagnose IFIs early, improve patient outcomes, avoid drug resistance, toxicity and reduce the economic burden of secondline agents.

There has been a rising incidence of IFIs (7%-15%) especially IA in patients with HM in the recent years [10,11,12,13,14,15,16,17]. This has been attributed to use of intensive chemotherapy with prolonged and severe neutropenia, extensive use of yeast-active prophylaxis (fluconazole) and large-scale construction work in the hospital premises (as was in our case). Performing BAL, FNAC/biopsy in patient with thrombocytopenia and neutropenia may be associated with complications. S-GMI assay was not available. Hence most of the IFIS were classified as possible (55/98), out of which 49.1% (27/55) were highly suggestive of IA. Our findings are similar to those published by Gupta et al [18]. The authors point out the impact of construction work in and around the hospital; with diagnostic facilities similar to ours, they too recorded a high incidence of IA, most of which were classified as possible IFIs viz. out of 60 IFIs, 56 were possible and 44% (25/56) were suggestive of IA. Ghosh et al, reported a lower incidence of IFIs (30%), most of which were possible IFIs (20.5%). They also recorded a case each of pulmonary IA and pulmonary mucormycosis. However, they had no cases of candidemia [19].

In order to prevent IFIs we have implemented the following measures: Prophylactic fluconazole is used only during ALL and AML induction. We use better tolerated regimes such as ATO+ATRA for AMl-M3 [20], TKIs with corticosteroids for Ph+ ALL [21], LDAC/decitabine [22] as firstline therapy for elderly with AML. In order to prevent respiratory infections we restrict the number of visitors and implement smoking cessation. We do not encourage the use of face masks by providers and patients. The review presented by Sorensen et al. supports our view [23]. Baseline neutropenia, relapsed-refractory disease and prolonged and severe neutropenia post-chemotherapy correlated with a higher incidence of IFIs. We need to risk stratify our patients based on pre-treatment (high risk AML and ALL, baseline neutropenia, leukemia status, highly mucotoxic regimen, age, performance status, comorbidities such as diabetes mellitus and COPD, prior aspergillosis, building constructions) and post-treatment (severe and prolonged neutropenia, persistent lymphopenia, oral mucositis, central line, multisite colonization by Candida species) risk factors [24] and include mold-active prophylaxis. As we do not have s-GMI, we are unable to institute the policy of preemptive diagnosis-driven antifungal therapy (DD-AFT). Compared with empiric therapy, this approach was shown to reduce the use of antifungal and increase the rate of diagnosis of IA [25]. Hence, weekly s-GMI may guide preemptive therapy, diagnosis and duration of therapy of IA.

AmB is given firstline at 1 mg/kg/day.2cc of chlorpheniramine maleate IV and paracetamol 650 mg orally are given 30 minutes prior to AmB. AmB is given as an infusion in 500 ml of 5% dextrose over 3 hours, covered from light. After this we infuse one litre of normal saline with two ampoules of potassium chloride. While receiving AmB, the patients are monitored for chills, fever and treated symptomatically.

Serum creatinine and potassium are monitored on alternate days. AmB is discontinued and secondline antifungals started if serum creatinine rises above two times the baseline. In case of hypokalemia, intravenous and oral potassium supplementation is done.

Secondline antifungals are voriconazole (200 mg orally twice daily) or caspofungin (70 mg loading dose on day 1 followed by maintenance dose of 50 mg), in case of failure of AmB, suspected/proven invasive aspergillosis (IA) or renal derangement/severe hypokalemia due to AmB. We do not use combination therapy. They are continued for 2-3 weeks, until recovery of counts (ANC >1000/mm3 [4], resolution of signs of infection and negative blood culture in those with initial positive ones.)

Among the AEs of AmB, majority were hypokalemia (Grade-1 and 3) (45.8%), followed by IRRs (Grade-2) (34.4%) and renal impairment (Grade-2) (2.1%). Renal failure reversed with hydration and discontinuation of AmB. A study by Horwitz et al., reported a higher incidence of nephrotoxicity (13.6%), AmB discontinuation (18.6%) and lower incidence of hypokalemia (16.9%), IRRs (11.8%). They concluded that the clinic-economic burden of AmB associated AEs were manageable and total abandonment of AmB was unjustified [26]. We administered G-CSF 5mcg/kg/day if ANC < 100/mm3 and neutrophil recovery is not expected within 3 – 4 days. We do not remove central lines unless there is exit-site/port-pocket infection or if candidemia persists beyond five days of treatment [27]. These patients require removal of central line and 4-6 weeks of antifungal therapy. At present we treat suspected mucormycosis (sinonasal IFIs) with AmB alone. Surgical debridement of necrotic tissue and LAmB may improve outcomes [28]. We start antifungal therapy immediately and delay chemotherapy till IFI is controlled. In settings requiring urgent antileukemic intervention, cytoreduction can be achieved with oral hydroxyurea [4].

Review of this data revealed that IFIs contribute significantly to the mortality statistics in our hospital. The following methods have been proposed to improve outcomes: No attempt should be spared to exclude other causes such as incorrect diagnosis (pulmonary inflammatory immune reconstitution syndrome - PIRIS), co-existent tuberculosis and suboptimal dose of antifungals [4, 29]. Use of s-GMI will enable us to provide preemptive therapy. Normal s-GMI can distinguish PIRIS (worsening pulmonary infiltrates coinciding with neutrophil recovery) from IA [29]. Performance of weekly surveillance cultures from tracheal aspirates, urine and gut (oropharynx and/or gastric aspirates) will detect multisite colonization (>1 site) by Candida species, an important risk factor for the development of IFIs [24,30]. Every patient with suspected IFI must undergo contrast-enhanced computed tomography (CECT) of the abdomen to look for hepato-splenic candidiasis. These patients have high fever despite broad -spectrum antibiotics, abdominal pain and gastrointestinal symptoms maybe absent. CECT shows multiple hypodense nodular lesions or peripheral double –ring (target-like) lesions [31]. Oral corticosteroids can hasten clinical recovery if symptoms persist despite antifungals [32]. We propose to ensure availability of caspofungin, LAmB, voriconazole and posaconazole in the government scheme. This will widen our therapeutic options; we can start IV therapy and switch to an oral agent after improvement; provided the patient is compliant and gastrointestinal function is intact. In case of aspergillosis or fusariosis voriconazole may be used and posaconazole for mucormycosis. We can include mold-active prophylaxis for patients at a high risk of developing IFIs [4]. We plan to conduct limited post-mortem biopsies of bone marrow, liver and spleen to look for persistence of the underlying HM or IFI. Chamilos et al. identified IFIs in 314 of 1017 (31%) autopsies of patients with HM, of which only 25% had been identified ante mortem [33].Maintenance of data on febrile neutropenia and the spectrum of IFIs and yearly audit will be done.

Conclusion:

IFIs contribute significantly to treatment failure in acute leukemia. AmB is a reasonable firstline agent with manageable toxicities. Use of secondline agents based on pre and post-treatment risk factors and periodic assessment of clinical variables, microbial data and mortality due to IFIs will improve outcomes.

Abbreviations:

AE(s): Adverse event(s)
ALL: Acute lymphoblastic leukemia
Allo-SCT: Allogenic stem cell transplant
AmB: Conventional amphotericin-B deoxycholate
AML: Acute myeloid leukemia
ANC: Absolute neutrophil count
ATO: Arsenic trioxide
ATRA: All *trans* retinoic acid
BAL: Bronchoalveolar lavage
BFM-95: Berlin Frankfurt Munster protocol for ALL
CEBPA: CCAT-enhancer binding protein alpha
CECT: Contrast enhanced computed tomography
CTCAE: Common terminology criteria for adverse events
CXR: Chest X-ray
DD-AFT: Diagnosis driven preemptive- antifungal therapy
ELN: European Leukemia Network
EORTC/MSG: European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycosis Study Consensus Group (EORTC/MSG)
FLAG-IDA: Fludarabine, cytarabine, idarubicin, granulocyte colony stimulating factor
FNAC: Fine needle aspiration cytology
FLT3-ITD: fms-like Tyrosine kinase- Internal tandem duplication
G-CSF: Granulocyte colony stimulating factor
IA: Invasive aspergillosis
ICU: Intensive care unit
HDAC: High dose cytarabine
HDMTX: High dose methotrexate
HEPA filter: High efficiency particulate arrestance filter
HM: Hematological malignancies
HyperCVAD: Hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone
IFI(s): Invasive fungal infection(s)
LAmB: Liposomal amphotericin-B
LDAC: Low dose cytarabine
LRTI: Lower respiratory tract infection
NPM1: Nucleophosmin-1
s-GMI: Serum *Aspergillus* galactomannan index

Table 1: Patient demographics

	ALL (n=58)	AML (n=63)
Median age (Years)	20 years	29 years
Gender (M:F)	1.6:1	1.52:1
Duration of symptoms (Median days)	12	14
Risk stratification (%)		
Good risk	0	21 (32.3%)
Intermediate risk	47 (81%)	34 (52.3%)
High risk	11 (19%)	10 (15.4%)
Setting of induction (%)		
ICU	5 (8.6%)	4 (6.1%)
Acute leukemia ward	40 (69%)	43 (66.2%)
General ward	8 (13.8%)	10 (15.4%)
OPD	5 (8.6%)	8 (12.3%)

Table 2: Outcomes of induction treatment

		ALL (n=58) (%)	AML (n=63) (%)
Complete remission (CR)		49 (84.5%)	43 (66.2%)
Refractory disease		4 (6.9%)	2 (3.1%)
Induction mortality		5 (8.6%)	20 (30.7%)
Cause of induction mortality		ALL (n=5)	AML (n=20)
	Bleeding	1 (20%)	2 (10%)
	Sepsis	3 (60%) 2 were attributable to IFIS	18 (90%) 8 were attributable to IFIs
	Others	L-asparaginase induced fulminant hepatitis: 1 (20%)	-

Table 3: Grading of adverse events of Amphotericin B as per CTCAE version 4.03

n=96	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	Total

Hypokalemia	16 (16.7%)	5 (5.2%)	15 (15.6%)	8 (8.3%)	-	45 (46.8%)
Renal failure	-	2 (2.1%)	-	-	-	2 (2.1%)
Infusion related reactions	6 (6.3%)	27 (28.1%)	-	-	-	33 (34.4%)

Table 4: Risk factors associated with the incidence of IFIs:

	With all-category IFIs n (%)	**p value**
Total number of chemotherapy courses (n=178)	98 (55%)	
Pre-treatment risk factors:		
High risk acute leukemia (n=22)	8 (36.4%)	0.069 (Not statistically significant)
Baseline neutropenia (ANC <500/mm3) (n= 64)	25 (39.1%)	0.0017 (Very statistically significant)
Relapsed-refractory disease (n=6)	6 (100%)	0.0334 (Statistically significant)
Age ≥60 years (n=2)	2 (100%)	0.5023 (Not statistically significant)
Post-treatment risk factors:		
Prolonged and severe neutropenia (n=122)	53 (43.4%)	<0.0001 (Extremely statistically significant)
Oral mucositis (≥ Grade 3) (n=18)	6 (33.3%)	0.0781 (Not statistically significant)
Central line (n= 154)	89 (57.8%)	0.0783 (Not statistically significant)

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