SHORT COMMUNICATION

Invasive Fungal Infections in Acute Promyelocytic Leukemia on Dual Differentiating Agents: Real World Data

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Abstract Invasive fungal infection (IFI) in patients with acute promyelocytic leukemia (APL) is a common phenomenon in developing countries. In a systematic study (Dual Inducing Differentiating agents—Indian Trial: DID-IT) using dual differentiating agents (ATO and ATRA) in 98 APL patients at our center we report 18.3% incidence of IFI (n=18). Among all cases of IFI three were definitive, 14 were probable and one was possible IFI. We conclude that incidence of IFI in APL is affected by environmental and therapy related factors and mere usage of dual differentiating agents need not necessarily decrease the incidence of fungal infections.

Keywords APL · Fungal infection · ATO · ATRA

Correspondence Literature on incidence of invasive fungal infections (IFI) in acute promyelocytic leukemia (APL) is scarce, particularly in the real-world settings. Also, most of the reported literature is among patients induced with chemotherapeutic agents (Idarubicin) with differentiating agent (all-trans-retinoic-acid: ATRA). We assessed incidence of IFI among APL patients treated systematically with a protocol based therapy (Fig. 1) as per registered trial

(Dual Inducing Differentiating agents—Indian Trial: DID-IT) consisting only of differentiation agents (Arsenic Trioxide and All-Trans-Retinoic-Acid) irrespective of risk category [1, 2]. This study was conducted at a tertiary care center from North India. As the current trial was not designed to study the IFI, the data was not collected prospectively and observations collated at the end of the registered study to answer an important question.

Among 98 patients enrolled in our study, 18 patients had evidence of IFI (18.3%). The organism (*Aspergillus* sps) was identifiable in the case of 3 patients (2 postmortem and 1 antemortem). All these infections in our study occurred during the induction phase only, and were treated with Amphotericin B. Among our case series we had 11 deaths during the first 30 days of which 2 patients had evidence of invasive fungal infection. One of these patients died secondary to spontaneous differentiation syndrome but post-mortem incidentally revealed angio-invasive focus of *Aspergillus* in lung which though was not implicated directly as cause of death [3]. We had no cases of IFI during consolidation and maintenance suggesting the role of initial neutropenia in the causation of IFI. Most of the fungal infections in our settings were seen in high and intermediate risk patients (44.4 and 50% respectively). All patients were neutropenic at the time of the diagnosis of IFI (ANC < 1000). The site of infection was sinuses (11 of 18), followed by chest (8 of 18) in these patients. Galactomannan was done in all cases and was positive during the course of illness in 83.33% (15 of 18) patients. Among all cases of IFI three were definitive, fourteen were probable and one was possible cases as per the revised EORTC/MSG consensus group criteria [4]. The incidence of IFI is higher than tuberculosis (otherwise a common infection in Indians) in this group of patients as reported from the same center [5].

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Fig. 1 The figure illustrates the treatment protocol based on which the APL patients in this study cohort were managed

Literature on incidence of invasive fungal infections (IFI) in acute promyelocytic leukemia (APL) is scarce. Ghavamzadeh et al. [6] reported IFI as the cause of early death in 2% of APL in a trial involving single agent ATO. Tallman reported 8% IFI in patients treated with AIDA protocol [7]. Pagano et al. [8] reported invasive fungal infections (IFI) in acute promyelocytic leukemia (APL) from SEIFEM-D registry as 9.7%. But we have contrary experience of IFI among our APL patients. The incidence of IFI in our study mirrors the findings of other tertiary care centers in our country. Sharma et al. [9] have reported 36% suspected fungal infections during therapy of AML whereas it was 26% in APML. Isolated use of differentiating agents has not lead to decrease in the incidence of IFI in our study as suggested by Pagano et al. We compared our results with those among SIEFEM-D trial, who among the available literature are the sole investigators who have specifically designed study for identifying IFI in APL (Table 1). We report higher incidence of IFI (18.3%) compared to SIEFEM-D investigators (7%). Multiple factors behind the higher incidence of IFI in our study include: (a) Longer time to diagnosis from symptom onset (average symptom duration 43.28 days, median 30 days, range: 3–180 days, SD—35.77) due to delayed presentation to

hospital owing to poor education status (median—10th grade of education) and poor financial status (average monthly income—INR15140/-; range: 1400–150,000; SD: 23,603.89). (b) The performance status was poor (ECOG ≥ 2) in 66.2% of the patients (ECOG 0–1.5%, 1–32.3%, 2–27.7%, 3–13.8%, 4–24.6%) at the time of initiating therapy. (c) Longer time to hematological remission of 37d (mean—36.98 days, range: 14–74 days, SD—12.409) defined as ANC > 1500/ μ L, Platelet > 100,000/ μ L thus prolonged exposure of the neutropenic patient is exposed to environmental fungi for a longer duration before therapy. (d) APML patients are treated in a general ward, without HEPA filters, due to resource constraints. (e) The treatment related factors include use of antifungal prophylaxis. We used only fluconazole prophylaxis in all our patients whereas in SEIFEM-D trial, investigators used alternative prophylactic agents (posaconazole, amphotericin). (f) Additionally, we used prednisolone prophylaxis 1 mg/kg/day for differentiation syndrome which can be contributing to the higher incidence of IFI.

We conclude that incidence of IFI in APL is affected by environmental and therapy related factors and mere usage of dual differentiating agents need not necessarily decrease

Table 1 Comparison of parameters between our study with SIEFEM-D investigators

	Our study	Pagano et al.
Study population (sample size)	98	103
Median age (years)	33	50
Male/female	58/39	50/53
CVC (% of total patients)	78%	50%
Induction characteristics		
Induction therapy	ATO + ATRA (98)	ATRA + Idarubicin (90) ATRA + ATO (13)
Median duration of induction	52 days	14 days
Median duration of follow up	42 months	36 months
Antifungal prophylaxis		
Fluconazole	100%	32%
Itraconazole	0	12%
Posaconazole	0	37%
Overall mortality		
Overall mortality at 30 days	11 (11.2%)	8 (8%)
Overall mortality at 30 days due to IFI	0%	1 (1%)

the incidence of fungal infections. There is a definitive need for long term prospective studies to identify the risk factors and preventive modalities for IFI in APL patients.

Authors' Contributions All authors participated in the study, YU, PKK and PM analyzed the data and wrote the paper, SV and PM designed the research study and AC's laboratory performed fungal studies. All authors were involved in the management of the patients. YU and PM were involved in the manuscript preparation. All authors vetted the submitted manuscript.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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