Baseline Chest Computed Tomography for Early Diagnosis of Invasive Pulmonary Aspergillosis in Hemato-oncological Patients- a Prospective Cohort Study

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Abstract

Invasive pulmonary aspergillosis (IPA) has dire consequences in hemato-oncological patients. We report our experience with performing routine baseline chest computed tomography for early diagnosis of IPA. We found high rates of proven or probable IPA diagnosed on admission among patients with newly diagnosed acute myeloid leukemia.

Key words- invasive pulmonary aspergillosis, invasive fungal infection, baseline chest CT, acute myeloid leukemia, hematologic malignancy

Background

Invasive aspergillosis, most commonly invasive pulmonary aspergillosis (IPA), has replaced invasive candidiasis as the most common invasive fungal infection in immunocompromised patients, causing a significant part of fungal disease related deaths in this population [1,2]. Performing baseline chest computed tomography (CT) for diagnosing IPA is not a matter of common practice. We sought to evaluate the incidence of IPA at baseline among high-risk hemato-oncological patients, to assess risk factors for IPA among newly diagnosed patients with acute leukemia and to evaluate the characteristics of patients and infections with IPA at baseline vs. IPA acquired later during hospitalization.

Methods

We prospectively included adult patients with hematological malignancies admitted between October 2015 and February 2018 to Rambam Health Care Campus. All consecutive patients with newly diagnosed acute myeloid leukemia (AML) admitted for induction chemotherapy, patients with relapsed acute leukemia admitted for salvage treatment, and patients admitted for allogeneic hematopoietic stem cell transplantation (HSCT) were included in our study. During the period of July 2016 to April 2017 we also included patients admitted for autologous HSCT. Patients underwent baseline chest CT, ideally within the range of 30 days prior to admission (for elective admissions) and up to seven days after admission. All baseline chest CTs were reviewed by a radiologist and a specialist in respiratory medicine. Patients with significant pathological findings (solid or ground glass nodules with or without halo, alveolar or ground glass opacities, or combinations), underwent fiber-optic bronchoscopy with bronchoalveolar lavage (BAL) in an attempt to identify the pathogen. BAL fluid was sent for fungal stain, fungal culture, *Aspergillus* polymerase chain reaction (PCR), and galactomannan (GM) antigen testing, among other tests. We also evaluated GM in serum. The diagnosis of IPA was based on the proposed European Organization for Research and Treatment (EORTC) and the Mycoses Study Group (MSG) criteria [3]. For the purpose of the study we forwent the host factor, however clinical and microbiological factors were followed strictly. In here we report on probable/proven IPA only. Following the diagnosis of IPA, the patient was started on antifungal therapy, preferably voriconazole. Patients were followed for the duration of their hospitalization. We excluded patients with a prior diagnosis of IPA.

All patients were hospitalized in the hematology department of 23 single-bed, high-efficiency particulate air (HEPA)-filtered, positive-pressure rooms. Patients who were not diagnosed with IPA received anti-fungal prophylaxis with posaconazole or fluconazole. Serum GM was measured routinely twice weekly, and positive tests triggered chest CT examination. Patients with prolonged febrile neutropenia unresponsive to broad-spectrum antibiotic treatment were evaluated with repeat chest CT. Pathological chest CTs were subsequently evaluated with bronchoscopy and BAL, as above.

The incidence of IPA was calculated for each group. Risk factors for diagnosis of IPA at baseline were evaluated among patients with newly diagnosed AML. In addition, we compared all patients with IPA at baseline to those acquiring IPA during hospitalization and chemotherapy. We used a chi-square test for categorical variables and t-test for continuous variables. All the analyses were performed using SPSS Statistics version 25 (IBM corporation New York, NY, USA); $p<0.05$ was considered statistically significant. The study was approved by the local ethics committee.

Results

Two hundred and ninety-five patients were included in our study; 107 admitted for induction chemotherapy for newly-diagnosed AML; 24 admitted for salvage chemotherapy; 82 admitted for allogeneic HSCT; and 82 admitted for autologous HSCT. Baseline CT was done a median of four days after admission. Baseline chest CT was normal in 204 patients, and abnormal in 91. Of those, 49 patients had significant pathological findings and underwent bronchoscopy with BAL. A diagnosis of IPA on admission was made in 15 (15/295, 5%) patients. An additional 29 patients (29/295, 9.8%) were diagnosed with IPA subsequently during hospitalization. All 44 cases were probable, 40 had positive GM in BAL, eight had positive GM in serum and six had growth of *Aspergillus* spp. in fungal culture from BAL. In addition, 11 had positive *Aspergillus* PCR in BAL not used as a sole microbiological criterion.

Among 107 patients with newly diagnosed AML, 11 (10%) were diagnosed with IPA based on baseline chest CT and an additional 9 (8.4%) were diagnosed with IPA later while hospitalized. Among 11 patients diagnosed with IPA at baseline, the median duration of symptoms related to the hematologic malignancy was 14 days (range 7-120). Four patients had fever in the week prior to admission and three had respiratory symptoms. The median neutrophil count on admission was 900/μL and only three were neutropenic (<500/μL) based on automated blood counts on admission. None of these, or other clinical factors (Table 1A), differentiated significantly between newly diagnosed AML with and without IPA at baseline, although patients with IPA at baseline were older (65±8 vs 56±16, p=0.081).

Twenty-four patients were admitted for salvage chemotherapy for relapsed acute leukemia. Of them, one patient was diagnosed with IPA on admission and an additional four patients (16.6%) were diagnosed eventually. Of 82 patients admitted for allogeneic HSCT, three (3.6%) were diagnosed with IPA at baseline and 14/82 (17%) were diagnosed subsequently. In the subgroup of patients admitted for autologous HSCT no patient was diagnosed with IPA at baseline and 2/82 developed IPA during hospitalization.

Overall, compared to patients diagnosed with IPA during the hospitalization, patients diagnosed by baseline chest CT were more likely to have a newly diagnosed hematologic malignancy (11/15, 73.3% vs 9/29, 31%, p=0.008); to be admitted for chemotherapy compared to transplantation (12/15, 80% vs 13/29, 44.8%, p=0.073); and to be older (64±7 vs 51±15, p=0.004) (Table 1B).

Discussion

We performed a prospective cohort study designed to evaluate rates and risk factors for IPA at baseline among high-risk hemato-oncologic patients. Among 107 patients with newly diagnosed AML 18.7% (20/107) were diagnosed with proven or probable IPA at any time during the hospitalization for induction chemotherapy. More than half of these patients (11/20, 55%) were diagnosed on admission, prior to receiving chemotherapy or to exposure to the ward. No clinical features were detected that marked the patients with IPA on admission compared to those without. Among all patients with IPA, those presenting with IPA on admission were significantly older and more likely to have a newly diagnosed hematological malignancy than those acquiring IPA later in-hospital.

There are few published studies that assessed the value of baseline chest CT for early diagnosis of invasive mold infections among hemato-oncological patients. The most comprehensive was recently published by Ceesay et al [4]. They prospectively evaluated baseline chest CT among 198 high-risk hemato-oncologic patients and found that a pathological baseline chest CT and EORTC/MSG-compatible CT findings were associated with a hazard ratio of 2.52 (95% CI 1.27-5.03) and 4.67 (95% CI 2.04-10.75), respectively, for subsequent diagnosis of IPA. The median time for IPA diagnosis was 14 days. Patient population was heterogeneous, consisting mainly of heavily pre-treated patients. Two other studies retrospectively evaluated the yield of baseline chest CT among pre-transplant patients [5,6]. Both studies demonstrated a low yield, though study populations differed (one study evaluated children and the other adults) and patient assessment was not standardized.

Our study is the first to systematically assess the value of baseline chest CT for early diagnosis among high risk hemato-oncologic patients, and more importantly patients with newly diagnosed AML who were not previously treated. We routinely evaluated all pathological chest CTs using a standardized approach. In this report we included only proven or probable IPA, whereas in practice we also treat possible IPA. It is noteworthy that patient characteristics and risk factors for IPA were similar when including and excluding possible IPA. Nevertheless, including possible cases would increase the number of IPA cases on admission from 15 (5%), to 37 (12.5%).

There are several limitations to our study. First, this is a single-center study performed in a hospital with high *Aspergillus* endemicity [7], thus findings might reflect only local epidemiology, although the validity of our findings regarding baseline CT is more dependent on environmental than hospital epidemiology. We had few data available on risk factors for IPA on admission and the small sample size might have masked differences between patients with and without IPA on admission. Formally patients did not comply with the EORTC/MSG host criteria [3]. Nonetheless we hypothesize that the inherent immunodeficiency of AML and functional neutropenia are sufficient to render a patient susceptible to invasive aspergillosis. Lastly, our study design could not assess the impact of baseline CT screening on mortality, although it is plausible that earlier diagnosis and treatment would improve prognosis. A randomized controlled trial comparing patients undergoing baseline chest CT to those not having a CT is needed to answer this question.

In summary, screening patients with newly diagnosed AML using a chest CT promotes early diagnosis of IPA and early initiation of targeted therapy. We believe this strategy is worthwhile also in the era of prophylactic anti-mold treatment to allow

optimal therapy. As no signs or symptoms at presentation that predicted IPA were identified, we currently plan to screen all new patients. More studies in different settings and cost-effectiveness analyses are needed prior to broad implementation.

Notes

All authors report no conflicts of interest.

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Table 1A: Patients with newly-diagnosed AML with and without IPA at baseline			
	IPA diagnosed at baseline N=11	No IPA at baseline N=96	P value
Female (%)	6 (54.5)	49 (51)	0.826
Age y, mean ± SD	65 ± 8	56 ± 16	0.081
Diabetes (%)	3 (27.3)	17 (17.7)	0.427
Living in Haifa and suburbs (%)	4/10 (40)	36/95 (37.9)	1
Living in rural area (%)	0/10	5/95 (5.3)	1
Duration of HM symptoms prior to HM diagnosis d, med (range)	14 (7-120)	14 (0-120)	0.667
ANC on admission N, med (range)	900 (50-12340)	1360 (0-52100)	0.511
ANC<500 on admission (%)	3 (27.3)	33 (34.4)	0.747
Fever prior to admission (%)	4 (36.4)	21 (21.9)	0.279
Respiratory symptoms prior to admission (%)	3 (27.3)	21 (21.9)	0.707
Table 1B: All patients, IPA at baseline vs. acquired IPA			
	IPA diagnosed at baseline N=15	IPA diagnosed in-hospital N=29	P value
Female (%)	9 (60)	13 (44.8)	0.34

Age y, mean ± SD	64 ± 7	51 ± 15	**0.004**
Diabetes (%)	4 (26.7)	5 (17.2)	0.463
Living in Haifa and suburbs (%)	6/14 (42.9)	11/27 (40.7)	0.896
Living in rural area (%)	0/14	1/27 (3.7)	1
New HM diagnosis (%)	11 (73.3)	9 (31)	**0.008**
Disease status (%)			0.065
Induction	11 (73.3)	9 (31)	
Relapse	1 (6.7)	4 (13.8)	
HSCT disease free	1 (6.7)	7 (24.1)	
HSCT disease active	2 (13.3)	9 (31)	
Treatment (%)			0.073
Allogeneic HSCT	3 (20)	14 (48.3)	
Autologous HSCT	0	2 (6.9)	
Chemotherapy	12 (80)	13 (44.8)	
HM (%)			0.213
AML	13 (86.7)	14 (48.3)	
ALL	0	3 (10.3)	
MDS	0	4 (13.8)	
MPD	1 (6.7)	3 (10.3)	
LY & MM	1 (6.7)	5 (17.2)	
Fever prior to admission (%)	4 (26.7)	3 (10.3)	0.207
Respiratory symptoms	3 (20)	4 (13.8)	0.675

prior to admission (%)			
ANC on admission N, med (range)	1100 (50-12340)	1880 (0-25300)	0.128
ANC on IPA diagnosis N, med (range)	60 (0-12340)	0 (0-22620)	0.245
WBC on IPA diagnosis N, med (range)	730 (60-17260)	370 (10-36830)	0.053
Hemoglobin on IPA diagnosis N, med (range)	8.2 (6-15.3)	8.1 (5.2-11)	0.728
Platelets on IPA diagnosis N, med (range)	27000 (7000-170000)	21000 (3000-262000)	0.519
ANC<500 on admission (%)	4 (26.7)	5 (17.2)	0.464

ALL= acute lymphoblastic leukemia, AML= acute myeloid leukemia, ANC= absolute neutrophil count, HM= hematologic malignancy, HSCT= hematopoietic stem cell transplant, IPA= invasive pulmonary aspergillosis, LY= lymphoma, MDS= myelodysplastic syndrome, MM= multiple myeloma, MPD= myeloproliferative disease, WBC= white blood cells