

Diagnosis and Treatment of Invasive Fungal Infections in the Cancer Patient: Recent Progress and Ongoing Questions

Dimitrios P. Kontoyiannis^{1,2} and Thomas F. Patterson^{1,2}

¹Division of Internal Medicine, University of Texas M. D. Anderson Cancer Center, Houston; and ²Department of Medicine, University of Texas Health Science Center at San Antonio, and South Texas Veterans Health Care System

In the last 5 years we have witnessed further developments in diagnosis and treatment of invasive fungal infections (IFIs) that complicate cancer chemotherapy. In this brief overview, we highlight some advancement, discuss future directions, and unmet needs in this complex area.

Keywords. cancer; *Aspergillosis*; candidiasis; treatment; diagnosis.

ADVANCES IN DIAGNOSIS

The introduction of biomarkers for detecting invasive mycoses in routine practice has become a reality in oncology centers. Specifically, the detection of galactomannan (GM) and beta-D-glucan (BDG) for *Aspergillus* and *Candida*, respectively, in various specimens has permitted the reliance on more preemptive and less empiric antifungal treatment strategies [1]. The factors influencing the performance of GM assays in serum have been known from studies from the early 2000s [2]. In the last 5 years, however, we have seen a flurry of studies documenting the improved sensitivity, specificity, PPV, and NPV of GM in bronchoalveolar lavage (BAL) in high-risk cancer. In contrast to the experience of GM in serum, prior mold active prophylaxis or treatment does not appear to compromise sensitivity of GM in BAL [3]. Furthermore, GM assays in serum and BAL have shown to have complementary diagnostic and prognostic value in stem cell transplant recipients with invasive aspergillosis (IA) [4]. In addition, major promise has been shown with the detection of *Aspergillus*

antigen with novel techniques such as a lateral flow assay as a “point of care” test [5]. If validated by further studies, this approach would further simplify and increase detection. Overall, it is highly likely that increasing reliance of biomarkers would decrease the need for invasive diagnostic procedures such as biopsy in these high-risk populations where the bleeding risk is high due to common thrombocytopenia. Routine GM detection in BAL would benefit from standardization of procedures for bronchoscopy and BAL procurement. Such protocols have been described, but more work is needed in this area [6]. Finally, a positive GM in a patient at risk for invasive mold infections in general is not synonymous to IA, as several other endemic fungi and other hyaline molds such as *Fusarium* spp. could give a positive GM [7].

Although not specifically studied in cancer patients, BDG assays have been shown to uncover a sizeable portion of blood culture negative cases of invasive candidiasis (IC) [8]. For the patients with culture proved fungemia, the differential time to positivity (≥ 120 minutes between cultures drawn through the catheter and from a peripheral vein) were shown to be highly specific for catheter-related fungemia [9]. In addition, both serum BDG and GM kinetics while on antifungal treatment have been shown to be a good surrogate marker for response and their baseline value can be an adjunct factor for prognosis in IC and IA, respectively [10, 11].

In regards to other culture-independent diagnostic platforms, polymerase chain reaction (PCR) remains investigational, although progress has been made in

Correspondence: Dimitrios P. Kontoyiannis, MD, ScD, 1400 Pressler St, FCT 12.5069, Unit 1463, Division of Internal Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030 (dkontoyi@mdanderson.org).

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the standardization of this procedure that has several technical parameters that influence its performance [12]. However, limited progress has been made in the development of biomarkers for early detection of mucormycosis, an emerging and frequently lethal disease in patients with hematologic cancer [13]. A small yet promising study reporting a very good performance PCR assay needs to be further validated [14]. As cultures may be negative even in histopathology and cytology positive specimens and because histopathological and cytological appearance of invasive molds is not diagnostic for a specific mold, there is need for development of molecular probes for *in situ* hybridization [15, 16]. There has been some progress in this area; however, many unresolved issues remain: specifically, concerns regarding availability, sensitivity, reproducibility, accuracy, due to many variables. In addition, interpretive criteria for DNA sequencing are still lacking for rare fungi [17].

Finally, the field of biomarkers for early detection of IFIs would welcome further innovation. As such, recent reports used detection of volatile organic compounds in exhaled respiratory samples for earlier detection of IPA [18]. Also the introduction of miniaturized magnetic resonance nanotechnology [19] and the explosive importance of Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) as a novel diagnostic tool to rapidly and accurately identify clinical pathogenic yeasts and molds are expected to revolutionize fungal detection and identification [20] in the microbiology laboratory.

For early radiological detection of invasive mold infections (IMIs), realizing that imaging does not address the issue of specificity, some developments are worthwhile to mention. First, a single center experience with the use of angiogram computed tomography (angio-CT) that capitalizes on the angio-invasive nature of IMIs showed promising results for earlier detection of such infections [21]. Second, positron emission tomography/computed tomography (PET/CT) capitalizes on the fact that fungal lesions are highly metabolic and fludeoxyglucose (FDG)-avid and could be used in selected IMIs cases for “staging” of the extent of infection and as a factor influencing decisions to stop therapy [22]. Third, characteristic CT lesions such as the “reverse halo sign” have been reported to favor mucormycosis over IPA [23].

Advances in Treatment

In the last 5 years, few pivotal clinical trials focusing on cancer patients with documented IFIs have been reported. Limited studies reinforced the notion of comparable efficacy of echinocandins in cancer patients with invasive candidiasis (IC) [24]. Recent studies also highlight the fact that IA indirectly influences outcome due to the reluctance of hematologists in prescribing intensive chemotherapy for leukemia following the diagnosis of IA with resultant poorer outcome of the underlying hematologic disease—that “drives” the ultimate prognosis [25].

Two important multi-institutional prospective randomized trials have been recently completed and presented so far in abstract form. The first trial dealt with the difficult question of combination therapy. In a large multi-institutional, prospective randomized, double-blind study that compared voriconazole (VRC) + placebo to VRC + anidulafungin for treatment of IA, no statistically significant differences in primary endpoints were detected [26]. However, in post hoc analysis, in the subgroup of patients with diagnosis of IA established by detection of GM, the combination fared better. Further analysis is needed to understand the true impact of this observation.

The second trial reported the comparison of isavuconazole, an investigational triazole, to the “gold standard” VRC, for the treatment of IA. Isavuconazole has appealing features (intravenous and oral formulation, once a day administration, more predictable pharmacokinetic features than VRC, and potential coverage of Mucorales) [27]. Results presented in abstract form showed comparable efficacy of isavuconazole to VRC and less toxicity in patients with IA [28]. Isavuconazole might be an addition to our increasing armamentarium for the treatment and secondary prophylaxis of various IMIs.

The increased survivorship of cancer patients with various IMIs has created new problems: those of toxicities of certain triazoles [29–32]. Specifically, increased risk for squamous cell carcinomas of the skin and bone fluorosis has been reported with chronic VRC use, whereas all triazoles have been implicated with increased rates of peripheral neuropathy and important interactions with some chemotherapeutic agents such as vinca alkaloids and cyclophosphamide [30, 32].

The value of salvage therapies with immune adjunct interventions (eg, white blood cell transfusions for cytopenic patients, cytokines, various combinations therapies) remains uncertain in view of the many inherent biases in these type of studies [33, 34].

We clearly need more “pragmatic” trials and innovation in study design such as adaptive randomization, codevelopment of biomarkers and novel antifungal agents, and uniformity of criteria to assess radiological responses. Ultimately, there will still be uncertainty on the real impact of an intervention as we have poor understanding on what constitutes “failure” [34]. For example, autopsies, the “gold standard” to assess causes of death and attributable mortality, are at historic lows in terms of performance in tertiary care oncology centers [35]. Finally, risk assessment for management of documented or presumed IFIs patients with leukemia or stem cell transplant remains an art whose components are derived from the careful knowledge of the natural history of the patient’s underlying hematologic disease, comorbidities, and prior exposures to pathogens and antimicrobial therapies. This “qualitative” concept should be an integral part of the evaluation, as it allows the identification of patients suitable for more aggressive prophylaxis [36], preemptive and targeted

therapeutic approaches. It is clear that cancer patients do not represent a homogeneous group [37], and they are not at the same risk for life-threatening complications or IFI-related death.

Numerous current and future questions in diagnosis and treatment of IFIs in cancer patients remain. Future research should refine existing models of risk stratification to reliably identify risk for severe IFI, create criteria for safe early transition to ambulatory treatment in selected cancer patients and replace empirical therapy with fungus-specific, preemptive or targeted therapy. The continuing emergence of resistant fungal pathogens, partially as a result of selection pressures in patients with prolonged periods of immune suppression prevents the use of “standard regimens” applicable to all cancer patients with IFIs. In the ensuing decade, the tremendous improvements already seen are expected to accelerate and further improvements in the natural history of these infections will be realized.

Notes

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