Fungal Infections in Malignancy

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Fungal infections are more prevalent in cancer patients and are becoming an increasingly appreciated problem in recent times compared to the past[1] . Initially less frequent, they were believed to be associated with hematologic malignancies; but now are increasingly found in solid tumours as well undergoing chemotherapy, radiation therapy, organ transplantation and bone marrow transplantation[2]. There are multiple factors involved in the increasing prevalence of fungal infections in malignant disease like chronic debilitation/malnutrition, prolonged and frequent antibiotic therapy, qualitative and quantitative deficiency of T-cell/rnacrophage/monocyte/neutrophils, hyperglycemia, acidosis, extensive surgery, intensive/high dose chemotherapy, radiation therapy, disruption of oropharyngeal/gastrointestinal mucosa, disruption of skin layers, tissue damage, organ transplantation, bone marrow transplantation, corticosteroid therapy, parenteral hyper-alimentation, mechanical obstruction/stasis and indwelling catheters[1-6]. The single most important predisposing factor, in these cases, is neutropenia which determines the susceptibility for fungal infections[1,7-9]. The fungal infections encountered in order of frequency amongst cancer patients are candidiasis, aspergillosis, cryptococcus, muconnycosis, Trichosporon beigelii, Fusarium spp, Geotrichum candidum, Curvalaria spp, Bipolaris spp, Pencilliurn spp, Rhodotorula rubra, Pseudallescheria boydii, Pichia farinosa, Tomlopsis pintoloppesii. Saccharomyces cerevisiae and Cunnighamella bertholletiae3. These flingal infections can be classified in three groups. First group include Histoplasma capsulatum and Coccidioides immitis which are frequent in normal host causing a self-limiting infection but can pose a significant threat in immunocompromised ones. The second group causes only a superficial self limiting infection in normal host, but cause a major visceral/disseminated infection in compromised patients. This group includes Candida spp, Cryptococcus neoformans and Aspergillus spp. The third group comprise of infrequent, recently recognized fungi which are likely to become morn frequent and even more threatening in future[3].

It is difficult to obtain an accurate figure of true frequency of fungal infections because of non-availability of complete clinical infonnation, undetermined size of risk population, cases remain undiagnosed till autopsy (which is not routinely perfonned in Pakistan), many cases are treated empirically with amphqtericin without a fungal infection ever confirmed. Candidiasis incidence is reported to be from 7%-16% in malignant disease, being more frequent in leukemia and lymphorna as compared to solid tumours and alone it accounts for morn than half of the fungal infection in malignancy10. The organs involved in disseminated fungal infection may include gastro-intestinal tract, liver, spleen, kidneys, heart, lung, nervous system and bone marrow[1,11,12]. This can cause laryngitis, pyelonephritis, peritonitis, arthritis, osteomyelitis, myositis, hypersplemsm, endocarditis, skin nodules, pneumonia, meningitis, cerebritis, opthalmitis and hepatic abscesses[13]. Host defense against fungal infection essentially comprise of cellular elements (lymphocyte, neutrophil, macropliage), humoral factors, serum iron, serum copper, iminunoglobulin and complement[10,14,15]. This host defense is severely and irreparably impaired in malignancy by a multitude of factors augmenting each other[1-3,6].

Management of these fungal infections in cancer patients is exceptionally difficult and often frustrating because establishing diagnosis is not that easy, usually available antifungals are not that effective and most of thc antifungal have serious toxicities[1]. The drugs available are amphotericin B, micoconazole, ketoconazole, flucytosine, fluconazole and intraconazole. Amphotericin B is the oldest, has a broadest

spectrum, but is highly toxic and lack desired level of efficacy in neutropenic patients16. Its liposomal preparation is safer, more effective, but expensive[17,18]. Miconazole is reserved to unresponsive çpatients or for those who cannot tolerate amphotericin[19] . Ketoconazole is active against many fungi, but it is not available in injectable form and lack effectiveness in neutropenic patients. It also interacts with antacids, cyclosponn, cimetidine and many other drugs[20,21]. Flucytosine alone is not that effective and is used in combination with amphotericin[22]. Fluconazole and itraconazole are newer drugs[23]. Fluconazole is highly effective in local and disseminated infection and penetrate all body fluids including CSF. It is generally well tolerated with a reasonable safety profile[24,25] . Iiraconazole has a wide spectrum with a minimal toxicity, highly lipophilic and protein bound, well displayed throughout the body and is highly effective[26]. Management and prophylaxis of fungal infection in cancer patients can never be complete without a discussion on role of cytokines. The human body employs over a hundred cytokines to regulate cell survival. differentiation, proliferation and physiological activation. These include interleukins[2,7,9,11]. crythropoietin, thrombopoietin, granulocyte macrophage colony stimulating factor, leukemia inhibitory factoç[1] granulocyte colony stimulating factor, oncostatin M, etc[2] These factors alone or in combination promote the proliferation and migration of granulocytes and monocytes in bone marrow[28,29]. These factors, when administered, are an important deterrent to fungal infection in malignant disease by restoring the neutrophil count and improving their efficiency by promoting the act of cell differentiation[1,9,30-33]. The arrival of new antifungal will hopefully improve the prognosis for cancer patients, having a much higher spectrum of activity, efficacy, with the least possible toxicities. Similarly a more judicious and prompt use of growth factors and cytokines is going to decrease the incidence, morbidity and mortality due to fungal infections in cancer patients. It is thus required to have a more liberal, prompt yet judicious usage of antifungals and cytokines incancerpatients. This need is more highlighted and stressed upon especially when more extensive and liberal surgery is becoming incorporated in the practice of surgical oncology, full dose and over-enthusiastic chemotherapy protocols are increasingly practiced, bone marmw transplantation becoming a routine and organ transplantation for cancer is just at the horizon. Above all, we am having a much better life expectancy and survival in cancer patients increasing the duration of exposure to fungi in these patients.

References

1. Young, L.S. Jnection in cancerpatients, In Cancer Treatment, eds. Haskell, CM. and Derek, J.S. Fourth edition, Philadelphia. USA., W.B. Saunders Company, 1995; pp. 206-215.
2. Bodey, AG. and Anaissie, E.J. Opportunistic fungsl infections: A major problem in immunocompromised patients, in Richardson, R.G.(Ed): Opportunistic fungal infections: Focus on Fluconazole. London, Royal Society of Medicine Services, 1989, pp. 1-16.
3. Anaissie, E., Bodey, G.P., Ksntarjian, H. t al. A new spectrum of fungal infections in patients with cancer. Rev. Infect. Dis., 1987;3:369-378.
4. Bodey, G.P. and Fainstein, V. (Eda): Candidiasis, New York, Raven Press, 1985; pp. 181-187.
5. Ellis, D.H. Clinical mycology: The human opportunistic mycosea. New York, Pfizer lnc., 1994;pp. 17-38.
6. Bow, E. 2. and Loewen, R., Cheang, MS., et al. Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia. Clininfect.Dis., 1995;21 :361-369.
7. Schaffner, A. and Douglas, H. Selective protection against conidia by mononuclear and against mycelis by polymorphonuclear phagocytes in resistance to aspergillus: Obacrvatioos on these two lines of defense in vivo and in vitro with human and mouse phagocytes. J.Clin.Invest,, 1982;69:6 17-631.
8. Rogers, T.R. Prevention of infection during neutropenia. Br.J. Haematol., 1991;79:544-549.

9. Howell, PB., Walters, P.R., Donowitz, G.R. et al. Risk factors for infection of adult patients with cancer who have tunnelled caotral venous catheters. Cancer, 1995;75:1367-1375.
10. Dreizen, S., McCredie, KB., Keating, M.J. eta!. Oral infections associated with chemotherapy in adults with acute leukemia. Postgrad. Med., 1982;71:133-146.
11. Bodey, G.P. Fungal infections in cancer patients. Ann. N.Y. Acad. Sci., 1988;544:43 1-442.
12. Myerowitz,R.L.,Pazin, G.J.,Allcn, C.M. Disseminatedcandidissis: Changes in incidence, underlying diseases and pathology. Am.J.Clin.Pathol., 1977;68:29-38.
13. Louria, D.B., Stiff, D.P. and Bennett, B. Disseminated moniliasis in adults. Medicine (Baltimore), 1962;41 :307-333.
14. Rogers, TS., Balsih, E. Immunity to candida albicans. Microbiol. Rev., 1980;44:660-682.
15. Lehrer, RI. and Clinc, M.J. Leucocyte candidacidal activity and rcaistsnce to systemic candidiasis in patients with cancer. Cancer, 1971 ;27: 1211-1217.
16. Christiansco, K.J., Bernard, EM., Gold, J.W.M. et al. Distribution and activity of amphosericin B in humans. J. lnfect. Dis., 1985;152:1037-1043.
17. Lopez-Berestein, U., Bodey, G.P, Frankel, L.S. et a!. Treatment of hepatosplenic candidiasis with lipoaomal-amphotericin B. J.Clin.Oncol., 1987;5:310-317.
18. Kruger, W., Stockschlader, M, Russmann, B., et al. Experience with liposomal amphotericmnB in 60 patients undergoing high dosetherapy and bonemarrowor peripheral blood stem cell transplantation. Br.J.Hematol., 1995;91 :684-690.
19. Jordan, W.M, Bodey, G.P., Rodriguez. V. et al. Miconazole therapy for treatment of fungal infections in cancer patients. Antimicrob. Agents Chemother., 1979;16:792-797.
20. Brinckcr, H. Prevention of mycosis in granulocysopenic patients with prophylactic ketoconazole treatment. Mycoses, 1983;24:242.
21. Fainstein, V., Bodey, G.P. Eltingh, et al. Amphotericin B or ketoconazole therapy of fungal infections in neutropenic cancer paticnts. Antimicrob. Agents Chemother., 1987;31:11 -15.
22. Bennett, I.E., Dismukcs, WE., Dama, R.J. et al. A comparison ofamphotericin-B alone and combined with flucytosine in the treatment of cryptococcal meningitis. N.Engl.J.Med., 1979;301 :126-131.
23. Saag, MS. and Dismukes, W.E. Azole anti-fungal agents: Emphasis on new triazolea. Antimicrob. Agents Chemother., 1988;32:1-8.
24. Van's Woos, J.W., Mastic, H. and van Furth, R. A prospective study of the efficacy of fluconazole against deep seated fungal infections. J. Antimicrobial Chemother., 1988;21 :665-672.
25. Samonis, G., Roisson, K., Karl, C. et al. Prophylaxis of oropharyogeal candidiasis with fluconazole. Rev.Infect.Dis., 1990;12 (suppi 3) 5369-8373.
26. Denning, D., Tucker, R., Hanson, L. et a!. Treatment of invasive aspergillosis with itraconazole. Am.J.Med., 1989;86:79 1-800.
27. Nicoa A. Nicola. Cytokine pleiotropy and redundancy: A vjew from the receptor, In polyfuetionality of hematopoietk regulators: The Metcal forum. Stem Cells, 1994; 12(suppl 1): 3-14.
28. Metcalf, D. and Burgess, A.W. Clonal analysis of progenitor cell commitment to granulocyte or macrophage production. J.Cell Physiol., 1982; 111, p.275.
29. Kouides, P.A. and DiPersio, I.E The hematopoietic growth factors, in Cancer treatment, eds. Haskell, CM. and Derek, J.S. Forth ed. Philadelphia, W.B. Saunders Company, 1995; pp. 69-77.
30. Young, N., Griffith, P., Brittsin, E. et al. A multicentre trial of antithymocyte globulin in aplastic anemia and related diseases. Blood, 1988;72: 1861-1869.
31. Antman, KS., Griffin, ID., Aelias, A. et al. Effect of recombinant human granuloeyte-macrophage colony-stimulating factor in chemotherapy induced rnyelosuppression. N.Engl.J.Med., 1988;3 19:593-598.
32. Clerk, S.C. and Kamen, R. The human hematopoietic colony- stimulating factors. Science, 1987;236: 1229-1237.

33. Sparano, J.A., O'Boyle, K. The potential role for biological therapy in the treatment ofbreast cancer. Semin. Oncol., 1992; 19:333-342.