Acute Myeloid Leukemia

Long-term survival in patients with acute leukemia and chronic disseminated *Candidiasis* despite minimal antileukemic therapy

Infections may require discontinuation of antineoplastic chemotherapy, which, in turn, renders patients vulnerable to disease progression or relapse. We identified six patients with acute leukemia in whom antineoplastic treatment had to be discontinued because of chronic disseminated candidiasis (CDC). However, despite minimal antileukemic treatment, all patients remained in complete remission. Immunologic mechanisms associated with CDC might have had an antileukemic effect.

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Infectious complications, in particular invasive fungal infections, remain a major cause of morbidity and mortality in patients undergoing treatment for acute leukemia.[1,2] In addition to the high risk of death due to the fungal infection itself, antileukemic treatment has to be discontinued in some patients for a prolonged period of time or even permanently, if the patient´s clinical condition deteriorates. This, however, makes the patient vulnerable to progression or relapse of the underlying malignancy. Among 2,000 patients treated in five hospitals for acute leukemia over the last 14 years, almost 40 patients were identified who developed chronic disseminated candidiasis (CDC). This is an uncommon form of *Candida* species infection that primarily involves the liver, spleen, and less frequently, kidney, lungs, and bone, and is usually restricted to patients undergoing intensive therapy for acute leukemia.[3] A striking feature of CDC is that it usually becomes clinically apparent when prolonged neutropenia has resolved, suggesting that immunologic mechanisms in the host´s response contribute to the pathogenesis of the disease. The mortality rate of CDC is still as high as 50%, and the optimal antifungal therapy, with a single agent or combination therapy, has yet to be defined as has the duration of therapy, which usually needs to be given for a prolonged period.[4,5] Although chemotherapy for the underlying malignancy should not be delayed because of the risk of disease progression,[6] antineoplastic therapy has to be interrupted in some patients or even discontinued permanently because of an unstable clinical condition, as was the case in six of our patients (Table 1). Inadequate treatment is, however, usually associated with a poor outcome because of disease progression or early relapse, and it is surprising that despite minimal antileukemic treatment, all of our six patients with acute leukemia and CDC are still alive and in complete hematologic remission (follow-up between 19 months and 14 years). Therefore, one is prompted to speculate whether CDC, as a chronic inflammation, might have positively affected the continuous complete remission. This had already been speculated for hepatitis in patients with acute leukemia, but the effect had been inconsistent when analyzing different groups of patients.[7]

Table 1. Clinical data of patients with acute leukemia and chronic disseminated candidiasis (CDC), in whom anti-leukemic treatment was discontinued because of poor clinical condition.

Gender and age at diagnosis	*Diagnosis and date of diagnosis*	*Treatment plan*	*Antileukemic therapy given*	*Status when therapy was discontinued*	*Organs involved by CDC*	*Diagnosis of CDC4*	*Antifungal therapy and duration5*	*Current status*
M, 14 months	AML M6 1/92	AML-BFM 93[1]	1.induction Part of consolidation	Remission	Liver, spleen	Histology	Ampho B, Itra 11 months	Alive, remission
F, 2 years	AML M0 12/94	AML-BFM 93[1]	1.and 2.induction Reduced maintenance therapy for 1 year	Remission	Liver, spleen	Histology	Ampho B, 5FC, Flu; 21 months	Alive, remission
F, 49 years	cALL 2/97	ALL/AUL[2]	Part of induction (three weeks)	Remission	Liver, spleen, lung	Histology	Ampho B, Flu, Itra; 16 months	Alive, remission
F, 29 years	T-ALL 3/98	ALL/AUL[2]	Part of induction (first phase and part of second phase)	Remission	Liver, lung	Histology Mol.biology	Ampho B, 5FC; 9 months	Alive, remission
M, 42 years	AML M1 11/00	Individual	Induction (idarubicin and cytarabine)	Remission	Liver, lung	Candida-mannan positive	Ampho B, Flu, Vori; 10 months	Alive, remission
F, 49 years	AML M4Eo 3/04	AMLCG[3]	1.and 2.induction	Remission	Liver, spleen, kidney, lung	Mol.biology	Ampho B, Vori; Flu; 11 months	Alive, remission

[1]In the clinical trial AML-BFM 93, 1.and 2.induction consisted of cytarabine days 1-8, idarubicin days 3-5 and etoposide days 6-8 (1.induction), and high-dose cytarabine days 1-3 and mitoxantrone days 4 and 5 (2.induction). The first part of consolidation therapy consisted of oral 6-thioguanine and prednisone, intravenous vincristine (days 1 and 8) and cytarabine (days 3-6 and days 10-13), whereas oral 6-thioguanine and 4-weekly subcutaneous cytarabine was given as maintenance therapy. [2]In the clinical trial ALL/AUL, induction therapy consisted of vincristine and daunorubicin days 1, 8, 15, asparaginase days 15-17, and prednisone days 1-17 (phase 1) and of 6-mercaptopurine, cyclophosphamide, and cytarabine (phase 2). [3]In the clinical trial AMLCG, induction therapy consisted of two cycles of idarubicin days 1-3, and cytarabine days 1-5. [4]In all patients, typical lesions in liver and /or spleen were demonstrated by ultrasound, computed tomography or magnetic resonance imaging, and the level of alkaline phosphatase was elevated. As indicated, histopathologic examination showed yeast cells and/or Candida-DNA was found by polymerase chian reaction in the biopsy specimen (Mol. biology). One patient had a positive serum titer of Candida mannan. According to recently published consensus criteria, all patients with typical findings in imaging studies and positive histology are considered to have proven invasive fungal infection (first four patients), whereas the last two patients are considered to have probable invasive fungal infection.[18-5]Ampho B: amphotericin B; 5FC: 5-fluorocytosine; Flu: fluconazole; Itra: itraconazole; Vori: voriconazole.

It is known that cytokines participate in the critical pathways for the initiation and maintenance of immunity in response to systemic candidiasis. The dominance of either Th1 or Th2 CD4+ cells directly correlates with the outcome and severity of infection.[8] Studies in mice have shown that the development of a protective candicidal Th1 response requires the coordination of cytokines such as interferon (IFN)-γ, interleukin (IL)-2, and IL-12 in the relative absence of inhibitory Th2 cytokines such as IL-4 and IL-10.[9] A positive effect of granulocyte colony-stimulating factor (G-CSF) and IFN-γ on the host defense against *Candida spp.* has been demonstrated *in vitro*, whereas IL-10 impaired host immunity.[10,11] Similarly, animal models showed the importance of IL-1α, IL-1β and IL-18 in the host defense against disseminated candidiasis.[12,13] Interestingly, individual cytokines can produce opposing effects, depending on dose and timing of their participation in the immune response. For example, cytokine depletion *in vivo* revealed that neutralization of IL-4 is protective early in infection.[14] In contrast, neutralization of endogenous IL-4 in the late stage of infection significantly exacerbates otherwise self-limiting infections.

Besides participating in critical pathways for the initiation and maintenance of immunity in response to CDC, cytokines also play an important role in anti-tumor activity. For example, it was demonstrated *in vitro* that lymphokine-activated killer (LAK) cells which were generated with IL-2 are capable of eliminating small numbers of tumor cells in bone marrow without significant destruction of immature syngeneic stem cells.[15] In six patients who underwent autologous stem-cell transplantation, LAK activity in peripheral blood was increased for several months after the administration of LAK cells generated *in vitro* by IL-2 and GM-CSF in combination with IL-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) administration *in vivo*.[16] In addition, it was shown that CD4+ T cells in the peripheral blood of a patient diagnosed with lung cancer were able to orchestrate the suppression of autologous tumor xenografts. The suppression was indirect because the tumor cells were MHC class I and II negative, and it was dependent on human IFN-γ and IL-12 produced by the co-engrafted patient´s peripheral blood lymphocytes.[17] It is conceivable that tumor killing occurs indirectly by cytokines that connect both the cognitive and innate immune systems in a complex network, which might also include other, still undefined molecules.[17] The studies also suggest that mechanisms of tumor killing may play a role in the control of minimal residual disease, but not in patients with a high tumor burden.[15,16] Interestingly, all the presented patients had achieved remission soon after the initiation of antineoplastic therapy (Table 1).

In conclusion, it can be speculated that immunologic pathways associated with CDC may have helped to keep patients with acute leukemia in continuous hematologic remission even when antineoplastic therapy had to be discontinued at a very early stage due to the patients' poor clinical condition. We recognize that we present a hypothesis that is supported by *in vitro* data and animal models, but that cannot be proven by clinical trials. However, further insight into underlying immunomechanisms might ultimately lead to new treatment strategies in acute leukemia, which could improve the outcome for subgroups of patients, for example those with minimal residual disease.

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