Mitigating Fear and Loathing in Managing Acute Myeloid Leukemia

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The contemporary care of patients with acute myeloid leukemia (AML) is made complex by potentially toxic treatments, continuously advancing science, aging patients, and individual treatment goals. By taking a survey of present-day approaches, we aim to dispel some of the trepidation surrounding that care of patients with AML. At the beginning is the initial presentation, and we will discuss whether or not AML should be considered a medical emergency. We will explore the complex realm of patient decision-making about initial therapy, including the intricate straits of patient–doctor communication, and available options for initial treatment. We will then address post-remission approaches and the controversies that lie therein, and survivorship issues. Finally, we will investigate the current role molecular assessments are playing in therapy recommendations.
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Hunter S. Thompson, the reporter most closely associated with the magazine *Rolling Stone*, was notorious for his brand of gonzo journalism, in which he blended fact and fiction in writing stories about the drug and music worlds that were unapologetically raw, honest, and which often included Mr Thompson himself. This style was exemplified by his book *Fear and Loathing in Las Vegas: A Savage Journey to the Heart of the American Dream*,[1] later adapted for a movie by Terry Gilliam.[2]

In this review, we will borrow from this technique to expose real-world facts and myths in managing patients with acute myeloid leukemia (AML). In further deference to Mr Thompson, we will name our patient HT. We will start with HT's initial presentation, and consider whether or not AML should be considered a medical emergency.

SO, YOU SAY YOU HAVE LEUKEMIA...

The classic, textbook prodrome to the ultimate diagnosis of AML involves 4–6 weeks of flu-like symptoms. What does that actually mean from a patient's perspective?

For a younger person, commonly (and somewhat arbitrarily) defined within the world of AML as someone <60 years of age,[3–9] this involves symptoms of fatigue, inanition or lassitude, poor appetite, fevers, and suffering work or home activities. After 2 weeks, on his or her own volition or more commonly at the prodding of a partner, HT goes to his primary care doctor or to an urgent care clinic, where he is told that these symptoms are consistent with a virus, and to return if they don't resolve in another week or two. This happens, at which point a complete blood cell count is drawn and a prescription for antibiotics is given. That night, or the next day, an ominous phone call describing "abnormal labs" takes place, and HT is referred to either a hematologist or to an emergency room, and the word "leukemia" or "cancer" is first spoken. If in an emergency room, the person delivering this news often is ill-equipped to provide much more meaningful information, and might advise HT that he should get "his affairs in order," as leukemia does not exactly have the best street credibility. It is at this point that HT is referred for inpatient confirmation of the diagnosis and AML therapy.

In an older adult, symptoms may be much more subtle, as most cases of AML in this population arise from a known or unknown antecedent hematologic disorder, such as myelodysplastic syndromes (MDS).[10–13] In this scenario, HT may complain of fatigue or lassitude for months, and may start to take a nap every afternoon. He doesn't act on this immediately, as it is insidious and may be dismissed as being normal, age-related fatigue, or perhaps some depression surrounding having recently retired. When he goes to his primary care physician to discuss his symptoms, his assessment may include a cardiac evaluation, Mini-Mental Status Examination, or a gastrointestinal workup if blood counts are obtained and anemia is identified. Only when these tests are found to be normal will HT be referred to a hematologist/oncologist for a bone marrow biopsy, where leukemia will be diagnosed.

How does this evolution to a definitive diagnosis affect a patient's receptiveness to a discussion about diagnostic

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approaches and therapeutic options? Particularly in a younger adult, the time from when leukemia is first suspected and treatment is started may be less than 48 hours, as across the entire Swedish population the median time was 3 days.[14] Compare this to the time a woman who is ultimately diagnosed with breast cancer has to consider her diagnosis and treatment: after noticing a breast lump and first worrying that she might have cancer, she schedules an appointment to see her primary care doctor, which takes 1–2 weeks. Her doctor confirms the presence of a lump, and schedules her for a mammogram and/or ultrasound, which takes another week, and a breast biopsy is then scheduled, 1 week after that. A few days after that, results return confirming breast cancer, and a discussion about treatment occurs, for a total of approximately 4 weeks. While no cancer diagnosis is easy to easy to hear, AML patients may thus be particularly prone to getting "stuck" in one of the Kubler-Ross stages of death and dying on the way to eventual acceptance, which can affect decision-making.[15,16] While there is no substitute for time to process the implications of this diagnosis, recognizing the current emotional state, then discussing this directly while providing a supportive environment, can aid in making collaborative treatment decisions that best align with the patient's goals and beliefs. The contemporary practice of medicine is increasingly a team effort, and consistent messaging from multiple caregivers can go a long way in helping a patient adjust to the new normal. Therefore, just as we are quick to give the vital stats of the disease and treatment, we should also relay the current emotional state of the patient when communicating with team members.

DECISIONS, DECISIONS, DECISIONS, AND GOALS

Once an AML diagnosis is confirmed, an informed discussion about treatment options must occur, quickly. In older adults with AML especially, therapies are generally divided into three categories.

HT might consider the first, aggressive induction chemotherapy, involving 7 days of cytarabine and 3 days of an anthracycline such as daunorubicin (so-called "7+3"). Complete remission rates with this approach range from 40%–60%, depending on patient selection and the definition of "older," while long-term disease-free survival at 5 years is approximately 5%–10%.[17–19] This must be weighed against a treatment-related mortality rate that can be as high as 25%, or even higher for those older than 75 years or with serious comorbid conditions, and immediate hospitalization lasting 4–6 weeks. The vast majority of younger AML patients, for whom remission rates can approach 80% and treatment-related mortality is $<10\%$, choose this route, and in these patients slightly better results can be achieved with increased doses of daunorubicin.[20] Still, this should not preclude a discussion of the other two options. Once a decision is made to pursue 7+3 therapy, it should not be delayed in younger patients, as shorter time to treatment has been associated with improved survival.[21] For older adults, on the contrary, time to treatment does not impact survival, and waiting to start therapy may allow for testing of genetic markers to determine better or worse risk prior to embarking on cytotoxic therapy.

The second category of therapy is what might be called low-intensity, or less aggressive, with standards including low-dose cytarabine, the only such approach that has been shown prospectively to prolong survival compared to best supportive care,[22] or treatment with a hypomethylating agent such as decitabine or azacitidine.

Decitabine was compared to a control arm on which 88% of newly diagnosed, older AML patients received low-dose cytarabine and 12% received supportive care alone.[23] Among 485 patients, the hazard ratio for death with decitabine compared to the control therapy was nonsignificant (0.85; 95% confidence interval 0.69–1.04, $P = .11$), despite the complete remission rate for the decitabine arm being higher (16% v 7%), along with the median overall survival (7.7 months v 5.0 months). A similar phenomenon occurred when clofarabine was compared to low-dose cytarabine, with a doubling in complete remission rate of 36% versus 18% but with no difference in overall survival.[24] In another study conducted in 488 older AML patients, azacitidine was compared to conventional care regimens, including 7+3, low-dose cytarabine, or best supportive care.[25] The median overall survival for patients treated with azacitidine was 10.4 months, compared to 6.5 months for patients receiving conventional care, which was not a significant difference. Thus, any of these approaches is acceptable, with low-dose cytarabine being less expensive and more convenient for the patient, as it can be administered at home.

The third category includes those patients who decline any disease-modifying therapy. One study of 2,657 AML patients derived from the National Cancer Institute's Surveillance Epidemiology and End Results program and Medicare databases and diagnosed from 1991–1996 showed that this group actually represents the majority (70%) of older AML patients.[26]

The choice HT makes about which therapy to pursue centers inevitably on his goals of treatment, and the initial discussion about therapy should be framed around this. Patients who choose the first category, of 7+3 therapy, are making a clear statement about their goals: they are willing to accept a high risk of treatment-related morbidity and even death for the chance to achieve a durable remission, and perhaps even cure.[27] Choosing intensive chemotherapy is consistent with goals of care in patients who ultimately want to undergo hematopoietic cell transplantation (HCT) also, as this approach maximizes the chance of a complete remission, the most desired state to precede a transplant.

For the second category of treatment, HT is clearly balancing quality with quantity of life. While he accepts