

Knowing is Half the Battle in the Genetics of Acute Myelogenous Leukemia

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In 1971, President Nixon signed into law the National Cancer Act, also known as the “War on Cancer,” with the intention of determining the biological underpinnings of cancer formation and thus strengthens our nation’s efforts to cure cancer. Since that time, researchers and clinicians have made significant advances in the diagnosis and treatment of many cancers, leading to decreased mortality rates in many neoplastic malignancies. However, in the past 40 years, little to no significant improvement has been made in the treatment of acute myelogenous leukemia (AML). The only new drug to be developed, Gemtuzumab ozogamicin, approved by the Food and Drug Administration in 2001, was subsequently withdrawn from the market due to increased mortality in post-marketing trials [1]. After investing billions of dollars in research and enrolling thousands of patients in clinical trials, we have learned that AML is not a single disease, but a heterogeneous genetic disorder, with no two cases being exactly alike [2].

During our formative years in high school and college, many of us read the “Art of War” by Sun Tzu. In this book, one of the most profound and seminal sections state, “So it is said that if you know your enemies and know yourself, you can win a hundred battles without a single loss. If you only know yourself, but not your opponent, you may win or may lose. If you know neither yourself nor your enemy, you will always endanger yourself”. Our collective “war on cancer” has illuminated the wisdom of this statement, especially as it relates to the treatment of leukemias. In order to win the war against AML, we still require a greater understanding of both our capabilities and the enemies’.

The success that can be won through better knowing ourselves and our enemy cannot be more aptly expressed than by the story of chronic myelogenous leukemia (CML), one malignancy in which we can claim a victory. The initial breakthrough in CML was when Janet Rowley at the University of Chicago discovered a recurrent chromosomal abnormality (Philadelphia chromosome) associated with this disease [3]. This observation ultimately culminated in the development of the STI571 inhibitor, which blocked the abnormal tyrosine kinase BCR-ABL, the single abnormal protein that drives the genetic mechanism of CML. The drug designed to block this abnormal protein changed the face of a disease. While once a universally fatal diagnosis, CML has now been transformed into a chronic but manageable disease, like hypertension. This achievement illustrates how knowing yourself and the enemy can lead to a giant leap forward in diagnoses, rationale treatments, and improved survival rates [4].

Can lessons learned from this CML story be applied to AML? Does AML have the equivalent of a Philadelphia chromosome? The answer is currently no to both questions. At present, we still do not completely understand the disease process, and therefore do not know our enemy. Clearly, whatever we are doing is not working. However, we do know we are in desperate need of a new therapy.

What do we know so far about AML?

Traditionally, AML has been classified into various categories

according to morphology, but has been treated with the same chemotherapy regimens. In recent years, we have begun to recognize that AML is a heterogeneous disease. Although the variations appear to be the same morphologically under the microscope, more sophisticated genomic technologies have shown the contrary: that AML is composed of various diseases with completely different biological drivers and mechanisms [2].

The pace at which the classification and biological understanding of AML has progressed has been driven by the improvements made in genetic techniques. Sequencing of the human genome [5] has been completed, and the first AML genome [6] has been sequenced by Tim Ley’s group at the Washington University. This has given AML researchers unprecedented insight into a cryptic disease process. Ross Levine and colleagues from Memorial Sloan-Kettering Cancer Center have described many of the genes (e.g., FLT-3, NPM1, IDH, JAK2, and TET2) that are mutated in AML and have tried to find correlations between these genes and survival as well as trying to determine which of these mutations are drivers and which are passenger mutations [7]. These findings can be applied in the clinic; for example, the recently FDA approved JAK2 inhibitor, ruxolitinib, underwent clinical trials in 38 patients, 18 of whom had secondary AML and 10 of whom had *de novo* AML. The JAK2 mutation was observed in 12 patients, three with *de novo* AML, seven with secondary AML, and two with MDS. Complete remission (CR), partial remission (PR), or stable disease (SD) was observed in 15 patients, 12 of whom demonstrated SD. Of the three patients exhibiting CR or PR, all had secondary AML and 2 were positive for the JAK2 mutation. Ruxolitinib treatment in these three patients not only resulted in response, but a reduction in spleen size and quality of life improvements [8]. This illustrates the potential for targeted therapy so long as we can solve the problem of how to predict which patients will benefit from such targeted therapy, a problem that may be solved when we improve our understanding of the underlying disease biology.

While these studies have expanded our understanding as to the complex pathogenesis of AML, the sheer volume of disparate genetic alterations presents a daunting task for researchers – that is, which are the key drivers and regulators in need of the most focus. Furthermore,

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our lack of understanding regarding the underlying biology of this disease has rendered clinical researchers impotent and thus unable to exploit what appear to be clear genetic defects in front of our faces.

Researchers were fortunate in studying CML, which is driven by a single oncogenic event; the disease is clearly defined by this abnormality. This knowledge, in capable hands, led to the creation of a plan of action to inhibit the abnormal tyrosine kinase. However, the AML story is more complicated, and the drivers of this disease are unclear. Single-agent approaches to block known mutated pathways in AML have not been successful. Now, we have a better understanding of the complex mechanisms by which AML cells are driven and realize that a one-size-fits-all treatment approach will not be possible for all AML patient populations. For example, there have been some benefits to using FLT3 inhibitors in a small subset of patients with FLT3-ITD mutations, which represents a ray of hope and increases our understanding of the treatment of AML [9].

Unfortunately, using a targeted agent without truly understanding the biological significance of the mutation will lead to only a modest benefit in certain populations, as shown by our colleagues studying solid tumors. Bevacizumab, a VEGF inhibitor that has been associated with modest improvement in progression-free survival in many solid tumors, but has not shown any overall survival benefit [10]. Recent evidence has indicated that bevacizumab may decrease the delivery of chemotherapy to the targeted area and therefore decrease tumor cytotoxicity. In addition, there have been reports of a hypoxia-driven pathway that may make these tumors more aggressive. Given these new findings, it is imperative to truly understand the biological mechanism of targeted therapy and to have potent biomarkers that will predict treatment response before initiating therapy [11].

Another example of how having a thorough understanding of this disease can help win the battle is seen in the story of crizotinib, a tyrosine kinase inhibitor that targets the EML4-ALK fusion protein. The EML4-ALK fusion gene is found in 4% of patients with non-small cell lung cancer, a highly aggressive disease; however, the use of crizotinib in this population showed a 90% response rate with minimal toxicities [12]. This study may serve as a model for future oncologic care, which will involve not only an understanding of the abnormality causing the cancer but also a rationale as to how to target the specific malignancy.

The time has come to increase our understanding of our patient populations with AML and the genetic defects inherent within

each individual that is driving the clonal evolution of the disease. Furthermore, we need to develop targeted therapies by determining the appropriate biomarkers that will predict patient response to proposed treatments.

Now that genomic data are more economically feasible, they will presumably become more readily available, especially when the diagnostic workup of a patient with newly diagnosed AML includes whole-genome sequencing. All of this is leading toward personalized medicine, with the ultimate prize being a true understanding of our enemy in order to win a hundred battles without a single loss.

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