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Precision Medicine for Acute Myeloid Leukemia

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Abstract

The goal of precision medicine is to personalize therapy based on individual patient variation, to correctly select the right treatment, for the right patient, at the right time. Acute myeloid leukemia (AML) is a heterogeneous collection of myeloid malignancies with diverse genetic etiology and the potential for intra-patient clonal evolution over time. We discuss here how the precision medicine paradigm might be applied to the care of AML patients by focusing on the potential roles of targeting therapy by patient-specific somatic mutations and aberrant pathways, *ex-vivo* drug sensitivity and resistance testing, high sensitivity measurements of residual disease burden and biology along with potential clinical trial and regulatory constraints.

Keywords

Personalized Medicine; Precision Medicine; AML; Leukemia; Sensitivity; Screening; Measurable Residual Disease; Minimal Residual Disease; MRD

Introduction

Precision medicine can be described as an aspiration to personalize treatment based on individual patient-specific characteristics rather than reliance on a “one sized fits all” therapeutic approach[1]. Historically initial clinical successes in cancer medicine using cytotoxic chemotherapy in the 1940s to 1970s appropriately resulted in the predominant focus of the field becoming the adjustment of doses, timing and combinations into standardized regimens that would allow most patients to receive and tolerate clinically effective, potentially curative, therapy. In contrast, the period from the mid 1980s to the present day was arguably most remarkable for the wealth of molecular and genomic information generated regarding tumor biology together with the successful application of “targeted” antibody and molecularly targeted therapeutics. Following these periods of

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emphasis on “drug” and then “tumor” respectively, precision medicine now promises an era of focus on the individual patient.

Unlike the case of chronic myeloid leukemia where the pathognomonic abnormality also proved to be targetable with great success [2], dramatic improvements in clinical outcomes over the last thirty years in acute myeloid leukemia (AML) have been limited to the small subset of patients with acute promyelocytic leukemia (ie: also with a targetable pathognomonic abnormality). This lack of progress is perhaps best exemplified by the fact that the most commonly used induction regimen for AML has remained unchanged as a combination of an anthracycline and cytarabine (sometimes with a third cytotoxic drug). In contrast there has been considerable increase in our understanding of AML etiology and biology over this time period with molecular and genomic profiling providing considerable new useful information regarding AML biology and prognosis. It is now clear from large-scale cancer sequencing studies that the diagnosis “AML” is a catch-all term for broad set of myeloid malignancies with a diverse genetic etiology and considerable heterogeneity between patients[3], with oligoclonality within any individual patient, and differences seen between time points during treatment[4].

Targeting therapy to patient-specific somatic mutations

Re-tasking the technical capacity and expertise from the human genome and cancer genome atlas projects to expand cancer genomic sequencing efforts yet further to allow a “big data” systems based approach that links knowledge of germline variation and acquired somatic mutations with biological phenotype and clinical outcome data is intellectually appealing[1]. The early history of such an approach in AML over the past decade provides a roadmap of some of the major challenges remaining to be addressed. AML is a tumor where the sites of disease allow for straightforward and repeated sampling, and has been the subject of extensive genetic characterization at all stages of the disease[3, 4]. Unfortunately attempts to therapeutically target even the lowest of “low hanging fruit” such as the common driver mutation of the tyrosine kinase receptor FLT3 becoming constitutively activated by internal tandem duplication (FLT3-ITD) have been extremely disappointing with only transient clinical responses seen [5, 6]. Responses were seen not only in those with the FLT3-ITD mutation (53%, 24% CR) but also in those without (14%, 5% CR) this putatively predictive biomarker[5].

In an era where the focus is what is best for a particular individual human at that stage of their disease rather than searching for underlying universally applicable rules, the contribution of inbred experimental models to precision medicine is not obvious. Interestingly however, in the above example of FLT3-ITD, detailed mechanistic investigation has recently revealed that FLT3-ITD in combination with mutated TET2 can induce site-specific changes in DNA methylation and gene expression in leukemia stem cells (LSCs). These gain of function changes result in LSCs refractory to both cytotoxic and targeted therapy, with targeting of the mutated driver FLT3-ITD only able to transiently lower leukemic burden at the level of the bulk leukemic clone but unable to eradicate the disease[7]. This subtle mechanism, which near perfectly recapitulates the clinical reality, is not predictable solely from information derived from high-throughput DNA mutation

sequencing. It is becoming increasing clear that knowledge of the location of mutations within the hierarchical clonal architecture of AML will be important for selection of the most efficacious targets.

Ex-vivo veritas? Drug sensitivity and resistance testing

While the example of FLT3-ITD demonstrates we currently do not always have the mechanistic sophistication to intervene effectively with a rational AML therapy against a particular target or pathway, several investigators are attempting to overcome this limitation by instead focusing on an unbiased therapy screening approach [8–11]. This uses high-throughput methods to screen a library of drugs for the ability to preferentially kill ex-vivo AML cells from a particular patient compared with normal bone marrow. This "individualized medicine" approach has the advantage that any therapy[9], or combination of therapy[10], selected as a result of such a screen already has pre-clinical evidence as justification for that particular patient. This approach may also be used iteratively at different time points in treatment and to adjust treatment, either by re-screening after treatment failure and/or based on overcoming resistance mechanisms as highlighted by acquired mutations [9]. This may also help identify biomarkers of treatment failure. The disadvantages of ex-vivo drug sensitivity screening include: screening only for drugs with cytotoxicity will potentially miss effective agents with alternative mechanisms of action[12], assessment of unsorted AML may give an incomplete description of the role of clonal heterogeneity in drug sensitivity, and the exclusion of the potentially major impact of the bone marrow microenvironment[13]. Promisingly this approach will now be tested in concert with the genomic profiling described in the prior section, to create a new three-year multi-center clinical trial (B.Druker, Personal Communication). This novel drug development paradigm is predicated on the understanding that AML is not one disease, but a diagnostic term applied to a diverse collection of myeloid malignancies with different etiology and hence potentially differing susceptibilities to any therapy.

High sensitivity measurements of residual disease burden and biology

It is now clear that current AML response criteria inadequately stratify patients for risk of subsequent relapse and death [14]. It is clear however that detailed sequential information regarding the *amount of disease remaining* to treat is going to be as important as the *type of disease* to be treated in any truly precision medicine strategy for AML. Such high sensitivity tracking of AML residual disease will be useful not only in determining the *length of treatment* and the need for additional "maintenance therapy" after completion of standard treatment [15] but also the *type of treatment* based on the kinetics of disease reduction as a marker of therapeutic efficacy. Additionally, the clonal composition of residual leukemia during or after treatment may provide predictive information in the form of mutations, biology or phenotype known to be associated with response or resistance to a therapy or combination of therapy (as determined from the approaches described in the prior two sections) – to allow rational prophylaxis of relapse with those agents most likely like to be efficacious[16]. Many technical, logistical and behavioral challenges remain however to be overcome before AML "MRD" measurements are adopted as standard of care [17]

Powering clinical trials where the maximal sample size is one

The goal of precision medicine is to personalize therapy based on individual patient variation. Unfortunately the current regulatory drug approval and randomized double-blind clinical trial framework that relies on statistical comparisons between groups was “fit for purpose” in a time before[18] deep genetic characterization could divide apparently homogenous patient groups into millions of subgroups.

Each patient within a subgroup may have multiple dysregulated pathways, each pathway or mutation having several potentially active “targeted” therapies to be tested alone and in combinations[2]. This huge discrepancy between “the method” and “the need” becomes larger still when one recognizes the other potential variables to be considered; AML is a clonal disease with the predominant clone at presentation not necessarily reflective of that seen at relapse[4], the total burden of leukemia varies widely, even between patients in a clinical remission[14] and that the microenvironment may have significant impact on the sensitivity of tumor to therapy[13]. While a variety of novel clinical trial designs have been proposed (including basket, umbrella, and adaptive enrichment strategies[19]) it is clear that the combinational diversity of mutations seen within cancer, coupled with the wide range of potentially testable “targeted” agents with various degrees of specificity[20], mean that testing optimal therapy combinations personalized for any one patient is not practicable according to the current paradigm.

Conclusions

Survival rates have improved for younger patients with AML over the past thirty years, despite the lack of major improvements in AML therapy, often attributed to improvements in supportive care[21]. Outcomes are still suboptimal, particularly in older patients. It has been suggested that the lack of therapeutic progress in AML may be a consequence of our insufficient understanding of the biology of AML [22]. It is now clear that AML is a heterogeneous set of myeloid malignancies with the potential for intrapatient oligoclonality and with aberrancy possible not only at the level of mutated genomic sequence but also in terms of differential splicing, epigenetic regulation and chromatin modification. In this context precision medicine for AML will require knowledge not only of germ-line genetic susceptibility factors and tumor associated somatic mutations, but also correlation of biomarkers with response to (and failure of) agents that target defined pathways as tested both in clinical trials and *ex-vivo* assays, together with high sensitivity measurements of post-treatment residual disease burden and biology. Precision medicine for AML implies not only picking the right drug, or correctly characterizing the malignant clone, but picking *the right treatment, for the right patient, at the right time* – and iteratively repeating this process while monitoring for changes in disease burden and biology over time.

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