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Precision Oncology: Another Tower of Babel?

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I still remember being a young resident during my training in internal medicine at the beginning of this millennium. It was the time when I first heard about imatinib (Glivec®), a novel compound targeting the oncogenic kinase activity of the BCR-ABL1 fusion protein and leading to deep remissions in a substantial number of patients suffering from chronic myeloid leukemia (CML). Nowadays, we know that imatinib, as well as further generations of similar drugs, can promise close to normal life expectancy to CML patients and, to some of those, the privilege of long-lasting treatment-free remission (functional cure).[1]

After all, this pioneering success of imatinib was the reason I became a hematologist and I was proud in taking part in the scientific movement dedicated to precision oncology. However, today I know that the success of imatinib in oncology is not the rule but an exception. Single-driver neomorphic fusion proteins that are targetable with high specificity are rather rare in cancer. Most tumors have a long history of genetic evolution with unique trajectories of multiple acquired somatic driver mutations over time, making none the same as the other.[2]

In the last two decades, we embarked on using high-throughput sequencing in clinical practice for most of our oncological patients. This allowed us to get a deeper understanding of genetic oncogenesis and improve prognostication, as well as prediction of treatment responses. Today, most of the tumor genomes are characterized, and, indeed, we have identified some recurrent mutational patterns that allowed for refined genetic classification and prognostication but only exceptionally for genetically inferred targeting therapies. At the same time, we recognized that the clonal heterogeneity remains astonishingly high with a relevant impact on drug development, clinical trials and research costs.

Let me provide some examples in my field of research, namely myeloid neoplasms. An increasing number of genetically defined sub-entities characterize acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Pharma and research consortia are struggling to design sufficiently powered trials for genetic subtypes defined by specific mutations in the genes like *FLT3*, *IDH1*, *IDH2* and *TP53*. The number needed to screen for suitable patients expands exponentially with the increase of genetic heterogeneity. This phenomenon is paralleled by the requirement for more resources for the performance of clinical trials, as higher numbers of centers are required to reach the recruitment goal within a reasonable timeframe. Switzerland on its own, without international collaborations, will hardly be able to provide any relevant contribution to this development. Therefore, keeping access to the privileges of the European Union, as well as other international trading networks, is of vital importance not only for economic but also for academic reasons.

Moreover, targeting cells harboring specific mutations results in escape mechanisms emerging from resistant sub-clones, leading to a shift of genetic drivers. As such, genetically inferred targeting therapies will hardly provide curative potential in AML and all treatments generally step behind the dynamics of clonal evolution. This observation leads to two major conclusions: i) AML may be best treated before the emergence of higher clonal complexity, i.e., at earlier stages of MDS or even clonal hematopoiesis, and ii) clonal evolution under treatment pressure remains highly unpredictable in AML as in many other cancers. In line with these notions, drugs that are targeting signaling pathways and not primarily genetic lesions seem to achieve higher and longer remission rates (i.e., BCL2-inhibitor venetoclax). Nevertheless, similar conclusions apply, as clonal heterogeneity will find its way to resistance. Therefore, a dynamic adaptation to clonal selection seems to be required to fight cancer.

Indeed, our experience from the treatment of AML and MDS with allogeneic hematopoietic stem cell transplantation taught us that the replacement of the clonally affected hematopoietic stem and progenitor cell compartment requires the addition of an immunological-driven graft versus leukemia effect for the prospect of cure. However, we still need to learn many lessons before we can master the immunological control of cancer cells, which has evolved to recognize dangerous cells dynamically and generally agnostic of their mutational status. Although prognostication and monitoring of minimal residual disease (MRD) have substantially improved with genetic markers, our understanding of the impact of gene mutations on disease biology remains in its infancy.

Genetically inferred precision oncology reminds me a bit of the biblical mythology of the Tower of Babel. Expectations were high, very high, and the over-ambitious enterprise ended in increasing confusion (heterogeneity), a distraction from the essential (understanding disease biology) and the collapse of the tower (unachievable goals). Unfortunately, our confusion has even increased since the recent publication of two competitive classification systems, namely the 5th edition from WHO, and the international consensus classification (ICC).[3,4] As physicians and scientists, we have to remain committed to collaboration (exchange within national/international networks) and truth (elaboration of consensus based on scientific evidence). Let us hope that reasonable science will prevail before the tower of unachievable goals will eventually tumble down.

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