TECHNICAL REPORT

Novel Therapies Push the Agenda for Transformation of Historical Diagnostic and Management Approaches

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Advancements in healthcare research have led to significantly increased awareness of the biologies of disease. With technologies like next generation sequencing of genomes and transcriptomes leading us into the future on the diagnostic side, our ability to mass produce biologic therapies is transforming therapeutic approaches significantly.

With the availability of biologics that stimulate cell production, the entire management spectrum is significantly different from where we were just a decade ago. These changes have a very direct impact on hematology since almost all of the new therapeutic agents have either intentional or unintended impacts on peripheral blood cell counts. This phenomenon extends across the new drug classes, and includes the ESA's (Erythropoiesis Stimulating Agents), TPO Mimetics (Thrombopoietin Agonists), Immunotherapies, chemotherapies and drugs that modulate immune responses.

In spite of the rapid transformation of therapeutic options, the diagnostic approach in some commonly occurring clinical situations lingers in the past, as does the approach to clinical trials and the interpretation of outcome studies.

Some of the consequences of this "mis-match" are that we are puzzled by the "slow responders" to intervention, and therapy decisions are made without even attempting to understand the underlying pathophysiological mechanisms at work [1].

In thrombocytopenic patients for example, we typically have more than seven therapeutic approaches that can be taken, and the initial and subsequent therapy choices are made on very little clinical and diagnostic information. It is not routinely required for example to understand the extent of the splenic or hepatic sequestration of platelets prior to making a splenectomy decision [2]. There is no absolute requirement for understanding the anti-platelet antibody status before making a therapy decision, and there is no grading of the immune component, or of the ability of bone marrow to produce platelets.

Decisions are most often made based on the result of clinical trial data, with scant regard for understanding the pathophysiological mechanisms in the individual patient. In the age of "companion diagnostics" and customized therapy choices, this is surely set to change.

Clinical trial outcomes data is directly linked to the prevalence of certain pathophysiological mechanisms in the patient population being assessed. For example, if the overriding mechanism of thrombocytopenia in the patient cohort is hypoproduction, one can expect drugs that boost production to do better than other drugs in that patient population [3]. Now would be a good time to understand pathophysiological mechanisms of the disease prior to therapeutic intervention. Once intervention has started, it becomes more complex to assess, due to interference of the intervention on the underlying mechanism.

Patients with predominantly hepatic sequestration of platelets are less likely to respond to splenectomy than those with splenic sequestration. Another opportunity for diagnostic enhancement?

Do we not need some sort of quantitative or qualitative grading of anti-platelet antibody load in order to justify attempts to modify immunological aspects of platelet destruction?

How much of the hyporesponsiveness to therapies is a result of missed opportunities to directly target the underlying pathophysiological mechanism?

And how does one justify intervention as relates to safety, efficacy and financial aspects if we do not understand the mechanistic basis for the low cell counts?

How much of the hyporesponsiveness to therapy is a result of the mismatch of therapy mechanism versus pathophysiological mechanism?
In chronic disease states, is it not conceivable that mismatched mechanisms are contributing to resistance to therapy?
Or do we continue to justify cycling from one therapy choice to another, hoping to eventually find sustained response?
In anemia management, we see the same phenomena. Questions surrounding hyporesponsiveness to therapy, failed financial justification for physiologically inappropriate therapeutic intervention [4] and reliance on outdated diagnostic classification (anemia of chronic disease) and diagnostic tests (indirect and variable [5]).
A diagnostic label of Anemia of Chronic Disease is unhelpful as relates to pathophysiological basis of the anemia [6] or in terms of alignment with therapy options.
While it is true that short term correction of anemia is possible by intervening in any way (Iron, EPO and transfusion will all correct the anemia in the short term); how is it possible to justify the intervention from a safety, efficacy and financial perspective if the intervention is mal aligned with the underlying pathophysiological mechanism? And if the therapy choice is justifiable, is it not important to understand the underlying physiology first, and then explain that additional rationale for deviating from the physiological approach?
Historical diagnostic testing for iron dependent anemia has involved quantifying storage forms, transport proteins and receptors associated with iron cycling. By assessing cellular hemoglobinization, there is potential to include all upstream components of iron cycling that contribute to the rate of cellular hemoglobinization. This is potentially a much more direct approach to iron therapy alignment.
If one could dissociate hemoglobinization (Iron dependent) from erythropoiesis (EPO dependent), one might better align diagnostic information on the anemia mechanism, with therapy decisions on a physiological basis.
This approach is consistent with attempts to understand and customize management based on the underlying physiological process, and provides additional tools for assessing mechanisms and justifying interventions.
In drug development, only about 20% of drugs that pass the preclinical phase eventually succeed as clinically available therapies. This highlights the need for generally applicable biomarkers that can reliably detect dynamic cellular responses. The remaining 80% of unsuccessful drug developments are a financial burden for pharmaceutical companies and there is too little justification for early termination of developmental efforts. While some biomarkers are necessarily specific and molecular in nature, accurate immature and mature cell counts are potentially less sophisticated but more informative tools in assessing safety and efficacy during drug development.
By quantifying both immature and mature cells from the same cell line, one can get a first look at mechanisms, and potentially move to more specific second line diagnostic testing on the basis of the screen. The scale of automated cell counting is so vast that if it is possible to use the screening information to understand pathophysiology, the impact is potentially significant.

References

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