ASH 2014: A Mirror on Progress, Challenges, and Opportunity for New Therapies in Hematologic Malignancies

For the eighth consecutive year, my colleagues and I have had the good fortune to attend the Annual Meeting of the American Society for Hematology (ASH). Held this year in San Francisco, and attended by more than 18,000 people, ASH continues to excite and amaze me with the pace of progress of new therapies in many hematologic malignancies such as chronic lymphocytic leukemia (CLL) and multiple myeloma (MM), and the seemingly intractable nature of other illnesses such as acute myeloid leukemia (AML). The depth and breadth of our understanding of the biological complexities of hematologic malignancies, and what this new-found knowledge reveals about opportunities for development of new interventional therapies, is astonishing to witness. ASH truly brings together a powerhouse of clinical investigators to review, discuss and learn about these developments. What then stood out for our team in 2014? While the advances we've seen with agents such as Imbruvica, Zydelig (and the emergent ABT-199) are remarkable (and continue to offer expanded benefit across a range of tumours), the following items should be remarked.

Immunotherapies on the rise: Therapies designed to restart the body's own disease-fighting mechanisms are re-emerging as an increasingly promising avenue in oncology. Two notable "entrants" at ASH were the Chimeric Antigen Receptors (CARs) and Immune Checkpoint Inhibitors such as the PD-1 class. It will be interesting to see in 2015 if CARs in B-cell cancers, which show early encouraging clinical data, and the significant investments made into companies like Juno Therapeutics will deliver on their promise. For the PD-1 drugs such as Keytruda® (Merck) and Opdivo® (Bristol-Myers Squibb/ Ono Pharmaceuticals), it will be fascinating to see if their promise/approvals in solid tumours like melanoma will translate to benefits in hematologic cancer where ASH 2014 became a beachhead for this drug class. There was some promising early data among patients who have not responded to other therapies, most notably from the Phase Ib Keynote-013 study in Hodgkin's lymphoma patients who had relapsed/refractory disease, where Keytruda showed a 66 per cent response rate … in patients who had all failed on Adcetris, and 69 per cent response rate of those who had failed prior transplant. Similarly, early-phase studies with Opdivo showed an 87 per cent response rate, which manifested very quickly after initiation of therapy, in classic Hodgkin's lymphoma patients who had up to six prior therapies, a remarkable early showing in such a clinical setting. If the clinical benefits of PD-1 therapy are confirmed in several planned larger trials, then the designation of Breakthrough Therapy (e.g. for Opdivo) will be well-warranted. Translation of these benefits into other hematologic cancers is eagerly watched for in 2015.

New light in AML treatment? While AML has been the subject of intense clinical trial investigation for many years, 7+3 remains the clinical backbone of therapy, and many new agents have failed in Phase III in several AML settings. Is this landscape changing with a new approach? Certainly the IDH-2 inhibitor approach, championed by Agios (Cambridge MA) and supported by Celgene, offers new hope. AG-221 targets a genetic mutation in IDH-2 that prevents specific white blood cells from normal maturation, leading to development of acute myeloid leukemia and other blood cancers. Reports at ASH from Agios' early trials indicate that blocking IDH-2 led to complete or partial remissions in 56 per cent of advanced/relapsed AML patients, remarkable data in this advanced disease setting that historically has seen little progress. It will be fascinating to track the long-term impact of AG221 in treated patients and see data from expanded trials with this agent.

Gene therapy approach yields impressive data: Gene therapy has for many years offered potential clinical promise, but has been plagued by a series of practical and safety challenges. Is this now changing? Certainly the early data from Bluebird Bio's clinical trials in beta-thalassemia patients offer tangible promise. This disease, characterised by a reduction in hemoglobin and one of the most common genetic blood disorders, requires lifelong transfusions for patients, and patients left untreated die in their forties. Data presented at ASH this year showed that four patients who had been given a single therapy of Bluebird's LentiGlobin BB035 were essentially cured, after showing sufficient hemoglobin production to reduce or eliminate the need for transfusion support during follow-up between three and 12 months.

Excellence in education: A hallmark of ASH continues to be the high standard and utility of the educational programme. Nowhere was this more evident than in the coverage of MM, both at the Ham Wasserman lecture from Dr San Miguel and in the point/counter-point led by Drs Moreau and Richardson in the "Myeloma; Controversies in Therapy" presentations. It is remarkable to reflect on advances in the treatment of MM patients over the past decade; they are unprecedented by any measure – overall survival, time to progression, quality of life, treatment options – and have resulted in the incorporation of novel agents into treatment plans at various stages of the disease, as well as changing treatment paradigms. Novel mechanism of action drugs highly effective in MM, such as proteasome inhibitors (PIs) and IMiDs, have resulted in 1st, 2nd and now 3rd generation agents, improving on effectiveness and toxicity profiles of earlier agents. In addition, options for front-line or salvage therapy use of ASCT are now being considered, with evaluations of long-term maintenance therapy under active investigation. From the perspective of patients who have a very active and engaged advocacy community, the outlook is bright. Is it getting brighter yet? Certainly the addition of CD38 monoclonals showing promise in clinical trials (e.g. BMS'/Abbvie's Elotuzumab) and newer HDAC inhibitors, such as Acetylon's Ricolonistat, continue to add promising clinical data to the armamentarium physicians may be able to offer their myeloma patients.

Tracking all of these advances into 2015 will be fascinating, and seeing these novel developments pull through from clinical research into clinical practice will be one of the best gifts that 2015 can bring to the many patients afflicted with these biologically complex hematologic diseases.

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