One disease, many faces

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Disease staging has been an integral component of cancer management and has traditionally been intended to serve two purposes – patient prognostication and making decisions regarding management. In hematologic malignancies, staging systems were initially designed more for predicting outcomes and were less focused on guiding treatment. The original Durie-Salmon staging system for multiple myeloma (MM) was developed for measuring 'tumor burden' and served primarily as a prognostic tool (Table 1).[1] Subsequently Greipp and colleagues developed the International Staging System (ISS) which was rapidly accepted by the field given its simplicity using easily available laboratory variables – serum albumin and serum β_2-microglobulin.[2] It divided patients into three relatively equal groups with different survival, making it an essential prognostic tool in the clinic and was also rapidly integrated into clinical trials allowing comparisons across trials.

Since the introduction of the ISS, a deeper understanding of disease biology and development of new therapeutics has led to a 3- to 4-fold improvement in survival in MM, highlighting the heterogeneity in outcomes, with genetic alterations emerging as the main driver of these differences.[3] Given these, it became clear that any risk stratification system will have to account for tumor genetics. The Revised International Staging System (RISS) integrated high-risk abnormalities, i.e., t(4;14), t(14;16), and del(17p), as well as serum lactate dehydrogenase level, another marker of high risk, into the ISS (Table 1).[4] With increasing appreciation of the spectrum of high-risk genetic abnormalities in MM it became clear that the RISS had many flaws – not accounting for all the high-risk markers (chromosome 1q abnormalities, 1p deletion, mutations involving the *TP53* gene, etc.) and not accounting for the cumulative effect of multiple high-risk abnormalities, among others. The RISS was also rather lopsided, with over half of the patients in stage 2, obscuring the heterogeneity among them.

During the past decade we have developed a better understanding of the spectrum of recurrent abnormalities including trisomies of the odd numbered chromosomes and translocations involving the IgH region on chromosome 14 with recurrent partner chromosomes (4, 6, 11, 16, and 20), referred to as primary abnormalities, and many other changes such as del(17p), del(1p), 1q gain, 1q amplification, and chromosome 13 abnormalities, all of which are considered to be secondary abnormalities acquired during clonal evolution.[5] While trisomies (hyperdiploidy) are associated with a better outcome, the high-risk abnormalities resulted in a shorter survival, with different abnormalities demonstrating varying impact. In addition, molecular profiling approaches using RNA expression in myeloma cells have led to the development of several expression signatures.[6] More recently, whole-genome sequencing approaches have identified a set of recurrent mutations that appear to increase in frequency with disease evolution and introduced another layer of complexity to prognostication. All these developments lead to an important question – can these additional disease characteristics enable better assessment of disease outcomes, and more importantly can they help us make therapeutic decisions?

The work published in this issue of *Haematologica* by Schavgoulidze and colleagues looks into this question.[7] The authors specifically examined the reclassification between the ISS and RISS, homing in on RISS stage 2 patients and demonstrating how this group can be segregated further. There have been other recent efforts to integrate known prognostic factors, further calibrating the system using different weights for the prognostic factors based on their observed impact on outcomes. The authors had previously described a prognostic index score.[8] Six cytogenetic abnormalities were identified as statistically relevant and the prognostic index score was computed as: 0.4 × t(4;14) + 1.2 × del(17p) – 0.3 × trisomy 5 + 0.3 × trisomy 21 + 0.5 × 1q gain + 0.8 × del(1p32). The score placed patients into three groups with different survival outcomes, also accounting for the good prognostic markers, an approach that other models had failed to incorporate. Recently, there have been two other large efforts to improve upon the existing approaches. The European Harmony project proposed a second revision of the ISS (R2-ISS) utilizing individual data from 10,843 patients with newly diagnosed MM enrolled in 16 clinical trials. A value was assigned to each risk feature according to its impact on overall survival (ISS-III: 1.5 points; ISS-II: 1 point; del(17p): 1 point; high lactate dehydrogenase: 1

Table 1. Staging systems for multiple myeloma.

Stage	Durie & Salmon	International Staging System (ISS)	Revised International Staging System (RISS)	Mayo Additive Staging System (MASS)	Second Revision of the International Staging System (R2-ISS)
1	All of the following: • Hemoglobin concentration >10.5 g/dL • Serum calcium value normal or ≤12 mg/dL • X-ray studies of bone showing normal bone structure (scale 0) or solitary bone plasmacytoma only • Low M-component production rate - IgG value <5 g/dL - IgA value <3 g/dL - Urine light chains <4 g/24 hours	• Serum albumin >3.5 g/dL • Serum β_2-microglobulin <3.5 mg/L	• Serum albumin >3.5 g/dL • Serum β_2-microglobulin <3.5 mg/L • No high-risk cytogenetic features • Normal serum LDH level	Total score =0 Factors scored ISS III = 1 del 17p = 1 High LDH = 1 t(4;14) or t(14;16) = 1 1q+ = 1	Total score =0 Factors scored ISS II =1 ISS III = 1.5 del 17p = 1 High LDH = 1 t(4;14) = 1 1q+ = 1
2	Neither stage I nor stage III A-No renal failure (creatinine ≤2 mg/dL) B-Renal failure (creatinine >2 mg/dL)	Neither stage I nor stage III	Neither stage I nor stage III	Total score =1	Total score =0.5-1
3	• Hemoglobin concentration <8.5 g/dL • Serum calcium value >12 g/dL • X-ray studies of bone showing >3 lytic bone lesions • High M-component production rate - IgG value >7 g/dL - IgA value >5 g/dL - Urine light chains >12 g/24 hours	• Serum β_2-microglobulin >5.5 mg/L	• Serum β_2-microglobulin >5.5 mg/L • AND one of the following (a) High-risk cytogenetics (t(4;14), t(14;16),del(17p)) (b) Elevated serum LDH level	Total score =2	Total score =1.5-2.5
4	NA	NA	NA	Total score ≥3	Total score =3-5

LDH: lactate dehydrogenase; NA: not applicable.

point; and 1q+: 0.5 points).[9] Patients were stratified into four risk groups according to the total additive score: R2-ISS-I (19.2%, 0 points), R2-ISS-II (30.8%, 0.5-1 points), R2-ISS-III (41.2%, 1.5-2.5 points), and R2-ISS-IV (8.8%, 3-5 points). Investigators from the Mayo Clinic took a similar approach and developed a simple additive staging system by assigning 1 point to each of the following high-risk abnormalities – high-risk IgH translocations [t(4;14), t(14;16)], 1q gain/amplification, chromosome 17 abnormality [(del)17p/monosomy 17], ISS-III, and lactate dehydrogenase above the upper limit of normal.[10] Patients were allocated to three groups in the presence of 0, 1 or 2 risk factors, resulting in a model that divided the patients into nearly equal groups with different outcomes. Other have explored integration of specific mutations to the RISS.

While these new approaches incorporate the major genetic abnormalities into the prognostic models, the incremental improvement, as highlighted by the C-statistic, has been minimal. As a result, the current systems including the recently developed ones are only able to define 60% of the variability we see in patients' outcomes. As Schavgoulidze and colleagues highlight in their discussion further refinements of the systems to attain more specificity will depend on the identification of other novel prognostic factors. Importantly, these efforts do not necessarily improve our treatment approaches. While several studies have shown that patients with high-risk genetic abnormalities may benefit from more intense therapies, offering a higher likelihood of getting to a state of negative measurable residual disease, as well as more intense maintenance approaches given for longer periods, they do not necessarily enable tailoring of therapy based on the underlying biology. This is important as we develop targeted therapies that appear to be more effective in certain molecular types, as with venetoclax in t(11;14) myeloma. Future efforts should not only be directed at developing systems that can define the outcomes with more specificity, but also allow us to make treatment decisions. It is possible that no one system may be sufficient, and we may have to settle for a risk stratification system for prognostication and an additional molecular classification that guides therapeutic decisions. Clearly, more work remains to be done.

Disclosures

No conflicts of interest to disclose.

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