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 hematological malignancies, staging systems were initially designed more for predicting outcomes and 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).\(^1\) Subsequently Dr. 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 ß2 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 ISS, a deeper understanding of disease biology and development of new therapeutics has led to a 3-4-fold improvement in survival in MM, highlighting the heterogeneity in outcomes, with genetic alterations emerging as the main driver.\(^3\) 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 [t(4;14), t(14;16),del(17p)] as well as serum LDH, another high-risk marker, into the ISS (Table).\(^4\) With increasing appreciation of the spectrum of high-risk genetic abnormalities in MM it became clear that RISS had many flaws—not accounting for all the high-risk markers (chromosome 1q abnormalities, 1p deletion, mutations involving TP53 gene, etc.) and not accounting for the cumulative effect multiple high-risk abnormalities, among others. Also, the RISS was 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 with recurrent partner chromosomes (4, 6, 11, 16, and 20)—referred to as primary abnormalities and many other changes like del17p, del 1p, 1q gain, 1q amplification, chromosome 13 abnormalities, all of which are considered to be secondary
abnormalities acquired during clonal evolution. While trisomies (hyperdiploidy) is 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 the myeloma cells have led to development of several expression signatures. 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 the prognostication approaches. All these developments lead to an important question – can these additional disease characteristics allow better assessment of disease outcomes, and more importantly can they help us make therapeutic decisions?

The work presented by Schavgoulidze and colleagues represent such an effort. They specifically examined the reclassification between ISS and RISS homing in on the RISS stage 2 patients and demonstrating how this group can be segregated further. There have been other recent efforts to integrate the 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 (PI). Six cytogenetic abnormalities were identified as statistically relevant and the PI was computed as: $0.4 \times t(4;14) + 1.2 \times del(17p) - 0.3 \times\text{trisomy 5} + 0.3 \times\text{trisomy 21} + 0.5 \times 1q\text{ gain} + 0.8 \times del(1p32)$. The score placed patients into three groups with different survival outcome, also accounting for the good prognostic markers, an approach that other models had failed to incorporate. Recently, two other large efforts have attempted to improve upon the existing approaches. The European Harmony project proposed a second revision of the ISS – R2ISS utilising individual data from 10,843 patients with NDMM enrolled in 16 clinical trials. A value was assigned to each risk feature according to their overall survival (OS) impact (ISS-III 1.5, ISS-II 1, del(17p) 1, high LDH 1, and 1q+ 0.5 points). 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 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 - HR IgH translocations [t(4;14), t(14;16)], 1q gain/amplification, chromosome 17 abnormality [(del)17p/monosomy 17], ISS stage III, and LDH > ULN. Patients were grouped into 3 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 patient outcomes. As authors of the current work highlight in their discussion further refinements of the systems to attain more specificity will depend on identification of other novel prognostic factors. More 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 allowing a higher likelihood of getting to an MRD negative state as well as more intense maintenance approaches given for longer periods, they don’t necessarily allow 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. The future efforts should not only be directed in 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 decision. Clearly, more work remains to be done.
References

Table 1. Staging systems for multiple myeloma.

|-------|----------------|-----------------------------------|---------------------------------------------|-------------------------------------|---------------------------------------------------|
| 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 β₂microglobulin < 3.5 mg/L | • Serum albumin >3.5 g/dL  
- Serum β₂microglobulin < 3.5 mg/L  
- No high-risk cytogenetic features  
Normal serum lactate dehydrogenase 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 III = 1  
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 β₂microglobulin > 5.5 mg/L | • Serum β₂microglobulin > 5.5 mg/L  
- AND one of the following  
  - (a) High-risk cytogenetics  
    t(4;14), t(14;16), del(17p))  
  - (b) Elevated serum lactate dehydrogenase level | Total score =2 | Total Score =1.5-2.5 |
| 4     | NA | NA | NA | Total score ≥3 | Total Score = 3-5 |