

Guidelines for Risk Stratification in Multiple Myeloma

Report of the 2008 International Myeloma Workshop Consensus Panel 2:

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1. Purpose of Risk stratification: The general purpose of risk stratification is not to decide whether to treat or not but to prognosticate.

- ◆ Decision to treat is based on the criteria set for the diagnosis of symptomatic myeloma which includes the CRAB criteria. Patients with clearly defined MGUS or SMM do not need initiation of therapy except on specifically targeted protocols. For example, if a patient with clear diagnosis of SMM has 17p- on FISH or del13 on cytogenetics analysis, it does not constitute an indication to start therapy. The risk stratification being described here is only for determining prognosis and stratification of treatment, rather than to decide whether to initiate treatment.
- ◆ There has been general consensus on the risk factors that help stratify patients receiving conventional therapeutic modalities. However, there are studies that suggest that Bortezomib, and to an extent Lenalidomide, may be able to overcome some of the poor risk features and achieve clinical benefit. Further studies are needed to decide on the ability of these agents to overcome the poor risk features. At the present time, it is important to stratify, but the available information does not indicate selection of therapies; e.g. if patient has t(4:14), it does not suggest that we should use a specific therapy or novel agent.
- ◆ Currently, to mandate definitive treatment according to cytogenetic abnormalities is premature, although there is emerging data suggesting that some of the novel agents could overcome the negative prognosis of the cytogenetics abnormalities.
- ◆ It is important to continue to assess the impact of risk factors with novel therapies and combinations. Clinical trials should be done based on risk stratification, to try and test whether certain patients benefit more or less from certain therapeutic agents or strategies.

2. Timing for Risk stratification

- ◆ **At Diagnosis:** There is consensus that the current risk stratification is applicable to newly-diagnosed patients. All current efforts are directed at stratification at diagnosis using the parameters obtained at diagnosis.
- ◆ **At Relapse:** There has been documentation of change in risk factors at relapse. For example, in one study the mean labeling index increased from 1% at diagnosis to 2.5% at relapse. If patients are followed individually, it is always higher at relapse versus at diagnosis. Similar data exists for detection of p53 deletion at relapse or disease progression compared to time of diagnosis.

- ◆ The evolving consensus is that if a patient acquires high risk features at relapse or progression, then that patient should be reclassified as having high-risk disease. For example if a patient was not detected to have t(4;14) at diagnosis but at relapse 20% cells show this change, then it is our consensus that this patient now should be reclassified as having high-risk disease.
- ◆ There is general consensus that genetic abnormalities characteristic of poor outcome at diagnosis may suggest poor outcome if detected at the time of relapse.
- ◆ Amongst current risk factors, re-determination of factors such as β -2M or ISS at relapse or at follow up is not currently considered as predictive of change in risk stratification. Role of level of serum LDH at relapse is less clear. A very high LDH is considered to represent proliferative disease. High LDH levels are uncommon in myeloma, but carry poor prognosis at diagnosis or relapse.
- ◆ Moving forward, an important goal for relapse trials would be to evaluate these and other risk factors at relapse, keeping in consideration the type of therapy used at relapse. This is important. as more novel therapies are becoming available and patients are living longer.
- ◆ In patients with relapsed disease, additional risk stratification criteria include type of response and length of response to prior therapy. Therapy-related poor risk features include progression while on therapy, and short duration of response. Unlike in the past, speed of response does not suggest overall outcome with newer agents
- ◆ If a patient already has an identified high risk feature at diagnosis, then there is no need to look for the same feature again. For example, if a patient at diagnosis has t(4;14), then one does not need to look for it again at relapse with same FISH probe. However, cytogenetic and FISH investigation should be performed at relapse to look for additional changes. If a patient is in a low risk group, then it is recommended that cytogenetics and FISH studies be performed at relapse for risk re-stratification

3. Is risk stratification specific for specific treatment

- ◆ There is general agreement that the risk stratification should be a global stratification, and not stratification for old versus new therapy or risk stratification for particular one treatment. We recognize that the risk features may be relevant to a given therapy. For example, when patients with del13 are considered to have poor prognosis, it is based on a large

number of studies focused on outcome following high-dose therapy and transplantation. However with use of novel agents, for example velcade, del13 does not seem to be predictive of high-risk. Thus risk factors for individual novel therapies are to be determined on an ongoing trial.

- ◆ There was a consensus that the high risk features will change in the future, with introduction of other new agents or possibly new combinations
- ◆ It is unclear whether risk stratification should change after patients receive certain treatments. For example, Bortezomib is able to overcome the poor risk associated with t(4;14); do we need to identify different risk factors for patients who are post-bortezomib treatment. The general opinion was that there is not adequate information to implement such a recommendation.

4. What risk factor to look for:

- ◆ There is a consensus that both cytogenetics and FISH play an important and independent role in risk stratification. Both FISH with specific markers and cytogenetics with specific abnormalities needs to be performed on bone marrow samples.
- ◆ Although detection of any cytogenetic abnormality is considered to suggest higher risk disease, the specific abnormalities considered as poor risk are: cytogenetically detected Chromosomal 13 or 13q deletion, t(4;14) and del17p; and detection by FISH of t(4;14); t(14;16) and del17p.
- ◆ High serum β 2M level and ISS stage II and III incorporating high β 2-M and low albumin are considered to predict higher risk disease.

5. What other risk factors to look for.

- ◆ A number of individual risk factors have been identified. However, there is in general emphasis to use a system that combines multiple factors, such as ISS. Some of these factors were considered in developing the ISS risk stratification systems.
- ◆ Due to lack of uniform availability of the data for analysis that led to proposal of ISS system, there are a number of factors which still may have a significant role in risk stratification as individual factors, e.g. LDH was not available for all patients and was not considered in developing ISS. However, in the limited patients that had this information LDH was found to have significant influence in identifying risk.
- ◆ Some of the features considered significant as individual factors are

LDH, IgA, extramedullary disease, renal failure, high serum free light chain and kappa/lambda ratio, plasmablastic disease, and plasma cell leukemia are useful under some circumstances but, their general applicability is unknown. Also it is very much a constellation of features that often determine high risk, rather than a single factor which may make it intermediate risk. Currently, unlike FISH/cytogenetics which may suggest a change in therapeutic approach to more aggressive treatment, no change in treatment approach is currently indicated based on such single higher risk features.

6. Consensus for evaluation of genomic changes

- ◆ There was a consensus that both cytogenetics and FISH play an important and independent role in risk stratification. Both have some favorable and some adverse risk features. Both highlight different disease parameters, and both need to be performed to have better understanding of the behavior and biology of the disease.
- ◆ Regarding cytogenetics, having any abnormality detected on cytogenetics by itself is a higher risk group. Within this group, patients with hyperdiploidy have better prognosis, while patients with del13, t(4;14) and del17p have poor prognosis.
- ◆ FISH data should be reported specifically for clonal plasma cells determined by surface marker or cytoplasmic immunoglobulin light chain expression, and not all cells. The positivity is to be determined by % positive cells that are above the individual laboratories' standard.
- ◆ No specific global cut off should be applied. It is unclear whether number of positive cells carries any different risk. For example, if a patient has 7% versus 57% cells positive for a specific FISH abnormality, the relative risk for both patients is considered same at the moment.
- ◆
- ◆ There is consensus that 1) detection of t(4;14), t (14;16), or 17p by FISH suggests higher risk disease; 2) del13 or 13q- detected only by FISH independently in the absence of other abnormality does not carry significant higher risk, while t(11;14) does not predict superior outcome; 3) There are some reports that 1q+, Del 1p may have clinical significance as a poor risk feature; however, the consensus is that the data is not yet adequate to suggest routine use of these FISH markers to predict prognosis.
- ◆ If a patient already has an identified high risk feature at diagnosis, then there is no need to look for the same feature again. For example, if a patient at diagnosis has t(4;14), then one does not need to look for it

again at relapse with same FISH probe; however, cytogenetic and FISH investigation should be performed at relapse to look for additional changes. If a patient is in a low risk group, then it is recommended that cytogenetics and FISH studies be performed at relapse for risk re-stratification.

7. ISS system

- ◆ ISS system incorporating serum albumin and β 2M is applicable as a prognostic system in majority of the settings. ISS is validated for conventional treatments as well as high-dose therapy. However, its validity with combination novel agent therapy still needs to be confirmed.
- ◆ Method used for measurement should be standard.
- ◆ ISS system, although extremely convenient for everybody to use, requires incorporation of additional myeloma-specific features to make it more robust or more applicable using the newer generation of drugs and studies.
- ◆ The ISS system is a baseline lowest common denominator, to be supplemented and not necessarily supplanted. There is a clear need and consensus to add cytogenetics/FISH or other markers to ISS.

8. Durie Salmon classification system?

- ◆ A clinical staging system at diagnosis using standard laboratory measurement, developed by Durie and Salmon, was predictive of clinical outcome after standard-dose chemotherapy. However, with the use of high-dose therapy and novel agents, the Durie-Salmon (DS) system is less predictive of outcome. This may be explained by the fact that the DS system is predominantly focused on tumor burden, and as these newer therapies are able to better reduce tumor burden, its significance has changed. There is increasing importance of tumor biology-related factors.
- ◆ DS system is still considered a means to measure tumor mass.
- ◆ There is general agreement that DS system can supplement the diagnostic criteria for myeloma such as CRAB (hypercalcemia, renal dysfunction, anemia and bone disease); however, if a patient has already been diagnosed as having symptomatic myeloma based on current criteria, then there is no need to use the DS system in regular practice for diagnosis. As only patients with symptomatic disease should be placed in clinical trials, reporting of DS system is not considered

essential. As Stage I represents early stage of disease, description of patients in clinical studies by DS staging system is encouraged. However, its routine clinical use is unclear.

9. Incorporate imaging – X-ray, MRI etc

- ◆ Number of bone lytic lesions, per DS system, is not considered of any prognostic significance.
- ◆ Although there are small single institution studies that have indicated that achieving MRI-directed CR has prognostic significance, this observation requires further studies to include imaging parameters in risk stratification or response definition.
- ◆ None of the imaging studies or results are currently recommended for inclusion in risk stratification

10. Inclusion of expression/genomic profile

- ◆ Expression profile data generated by a number of groups have been very helpful in identifying an expression signature that may identify a poor risk group. Shaughnessy et al investigated expression profile of myeloma cells in 532 newly-diagnosed myeloma patients treated on 2 protocols incorporating tandem autologous transplantation. Using log-rank tests of expression quartiles, 70 genes linked to shorter durations of complete remission, event-free survival, and overall survival were identified. The ratio of mean expression levels of up-regulated to down-regulated genes defined a high-risk score which was an independent predictor of outcome endpoints in multivariate analysis ($P < .001$) that included the ISS and high-risk translocations. A subset of patients with high risk score had a 3-year continuous complete remission rate of only 20%, as opposed to a 5-year continuous complete remission rate of 60% in absence of a high-risk score. Interestingly, multivariate discriminant analysis identified a 17-gene subset that performed as well as the 70-gene model.
- ◆ A second large study recently published by Decaux et al from the IFM group studied gene expression profiles of myeloma cells obtained at diagnosis in 182 patients and identified the 15 strongest genes to calculate a risk score associated with the length of survival. This analysis divided patients into high-risk group, characterized by the overexpression of genes involved in cell cycle progression and its surveillance, and low-risk patients, with hyperdiploid signature and heterogeneous gene expression. The results were confirmed in a test set, as well as independent cohorts comprising 853 patients with multiple myeloma. Overall survival at 3 years in a low risk or high risk

groups was 91% and 47%, respectively. These results were independent of traditional prognostic factors.

- ◆ It is interesting to note that although both these studies have included patients undergoing high-dose therapy, the 15 and 17 gene models do not share common genes. This highlights the complexity of biological behavior of the tumor and the fact that ultimate utilization of such expression data will require significantly more work. Functional commonality or functional association between these various genes needs to be considered in developing a more composite model. It also highlights the molecular redundancy in tumor cells driving their clinical behavior.
- ◆ The factors that require standardization are method used to assess expression profile, the data analysis technique, consensus and validation of genes to be considered important for risk stratification, and standardization of method to apply this definition to expression profile for a single patient.
- ◆ A more robust and comprehensive analysis is needed to analyze significance of stratification using CGH/ SNP array.
- ◆ In the future, a specific polymorphism may help identify patients with differential response profile and/or higher risk of toxicity. However, currently there is lack of data to propose any specific SNPs that can be utilized for such decision.

11. Consideration of risk factors in special therapeutic scenario.

- ◆ There is emerging data that allotransplant may have beneficial outcome in high-risk patients defined by cytogenetics/FISH. This data is limited and requires further confirmation. However, the group feels that allo transplant could be considered in this group of patients.
- ◆ Current level of evidence does not provide direction in deciding if a specific group of patients will benefit from maintenance therapy