Managing Myeloma

Revised International Staging System for Multiple Myeloma*

Multiple Myeloma staging and prognostic navigation tool

Developed in a large sample size of 3,060 patients, the revised international staging system (R-ISS) for multiple myeloma is a new risk-stratification algorithm with improved prognostic power compared to the three already widely used individual prognostic indicators it incorporates: (1) ISS (as determined by serum β2-microglobulin and albumin levels); (2) the presence of any one or more of three specific chromosomal abnormalities [del(17p), and/or translocation t(4;14), and/or translocation t(14;16)] as detected by interphase fluorescence in situ hybridization (iFISH); and (3) serum lactate dehydrogenase (LDH) level. In newly diagnosed multiple myeloma patients, the R-ISS allows for the identification of three distinct myeloma entities with significantly different survival outcomes.

Step 1: Determine the ISS stage of the patient

ISS Stage	Criteria
I	Serum β2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Not ISS I or ISS III Serum β2-microglobulin ≥ 3.5 mg/L but < 5.5 mg/L or Serum albumin < 3.5 g/dL
III	Serum β2-microglobulin ≥ 5.5 mg/L

Step 2. Assess risk according to chromosomal abnormalities by iFISH.

Risk	Criteria
Standard Risk	No high-risk chromosomal abnormalities
High Risk	Presence of del(17p), and/or translocation t(4;14), and/or translocation t(14,16)

Step 3. Assess risk according to serum lactate dehydrogenase (LDH) level.

Risk	Criteria
Normal	Normal serum LDH < the upper limit of normal as defined by the reporting laboratory
High	High serum LDH > the upper limit of normal as defined by the reporting laboratory

Step 4. Identify the R-ISS stage of the patient according to the three criteria determined in steps 1 to 3.

R-ISS Stage The new model for risk stratification for multiple myeloma	Criteria
I	ISS stage I and standard-risk chromosomal abnormalities by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk chromosomal abnormalities by iFISH or high LDH

With the new R-ISS stage, the prognosis of the patient by median survival [median progression-free survival (PFS) in months and median overall survival (OS) in months] can then be determined as assessed for the whole study conducted by the IMWG. Subgroup analysis data provides median OS by R-ISS stage for patients who received either primary therapies for transplant ineligible patients, primary therapies for transplant eligible patients, immunomodulatory drug (IMID)-based therapies, or proteasome-based therapies. See reverse side for R-ISS stage determination table with corresponding median survival data.

*Developed by the International Myeloma Working Group (IMWG)

Always discuss the option of clinical trial with your multiple myeloma patients.

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R-ISS Stage Determination Table with corresponding median survival.[1]

Prognostic Factors			*R-ISS*	Prognosis		Median OS in months based on treatment			
ISS Stage	Presence of chromosomal abnormalities by iFISH: del (17p), and/or t(4;14), and/or t(14;16)?	High LDH?	***New* R-ISS Stage**	**Median PFS months**	**Median OS months**	Non-transplant eligible based regimens	Transplant eligible based regimens	IMID-based regimens	Proteasome inhibitor-based regimens
I	N	N	**I**	**66**	**NR**	66	NR	NR	NR
I	Y	N	**II**	**42**	**83**	70	88	88	81
I	N	Y	**II**	**42**	**83**	70	88	88	81
I	Y	Y	**II**	**42**	**83**	70	88	88	81
II	N	N	**II**	**42**	**83**	70	88	88	81
II	Y	N	**II**	**42**	**83**	70	88	88	81
II	N	Y	**II**	**42**	**83**	70	88	88	81
II	Y	Y	**II**	**42**	**83**	70	88	88	81
III	N	N	**II**	**42**	**83**	70	88	88	81
III	Y	N	**III**	**29**	**43**	41	42	40	47
III	N	Y	**III**	**29**	**43**	41	42	40	47
III	Y	Y	**III**	**29**	**43**	41	42	40	47

NR=not reached, PFS=progression-free survival, OS=overall survival, LDH=lactate dehydrogenase, iFISH= interphasic fluorescence in situ hybridization

Reminder: According to the report of the 2009 International Myeloma Workshop (IMW) Consensus Panel 2 regarding guidelines for risk stratification in multiple myeloma, **the purpose of risk stratification is not to decide whether to treat or not to treat but to prognosticate.**[2]

WHY SHOULD WE RISK STRATIFY?[3] Patient counseling. One of the main reasons for assigning risk to each patient with a disease is to inform the patient of their prognosis. This is and still remains a very important reason for risk categorization and provides a framework for patient counseling, providing the answer to one of the most commonly ask question of 'How long do I have to live?', after someone is told of their diagnosis of cancer. This is no less true for the myeloma patient. The R-ISS is a simple and powerful prognostic staging system, and it should be incorporated into practice to stratify patients with newly diagnosed multiple myeloma effectively with respect to the relative risk to their survival. There is no evidence so far to suggest altering treatment or selecting a specific treatment based on risk groups with the exception that prolonged proteasome inhibitor-based treatment should be given to patients with t(4;14) and possibly 17p13 deletion.[3]

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[1]Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol*. 2015 Sep;33(26):2863-2869. PubMed PMID:26240224.

[2]Munshi NC, Anderson KC, Bergsagel PL, et al; International Myeloma Workshop Consensus Panel 2. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood*. 2011 May 5;117(18):4696-4700.

[3]Chng WJ, Dispenzieri A, Chim CS, et al;International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014 Feb;28(2):269-277.

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