Consensus Panel 2

Risk Stratification

Purposes

- Not to decide whether to treat or not
  - SMM with t(4:14) or del13 by FISH or on cytogenetics – Treat or not?
- To determine prognosis
- To stratify patients in trials
- To update prognostic factors in the era of novel therapies (thalidomide, bortezomib, lenalidomide)

Novel agents

- Preliminary reports suggest that Velcade® is able to overcome t(4;14) prognosis.

- Conflicting data on IMIDs.

- Currently, to mandate definitive treatment according to cytogenetic abnormalities is premature

- Further data needed for treatment recommendations

Time of assessment

At diagnosis

- The current risk stratification is applicable to newly-diagnosed patients the parameters obtained at diagnosis

- Serum markers

- Cytogenetics (Karyotype)

- FISH

Time of assessment

At relapse

- Evidence of change in risk factors at relapse. e.g. mean labeling index increased from 1% at diagnosis to 2.5% at relapse

- If a patient acquires high risk features at relapse or progression, then that patient should be reclassified as having high-risk disease. i.e. a patient without t(4;14) at diagnosis, at relapse has 20% cells +

Time of assessment

At relapse

- Same genetic abnormalities characteristic of poor outcome at diagnosis may suggest poor outcome if detected at the time of relapse.

- re-determination of factors such as b-2M or ISS at relapse or at follow up is not considered predictive of change in risk stratification.

- Role of f serum LDH at relapse is less clear.

Time of assessment

At relapse

- 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.
- Therapy-related poor risk features include length of response to prior therapy – ether progression while on therapy or short duration of response
- If a patient already has an identified high risk feature at diagnosis, then there is no need to look for the same feature again.

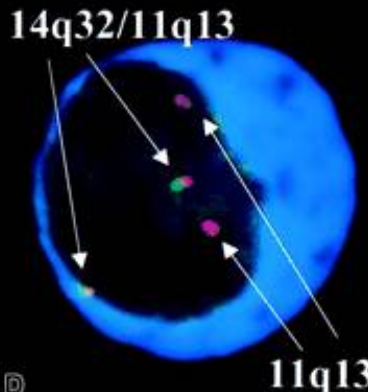
What risk factors?

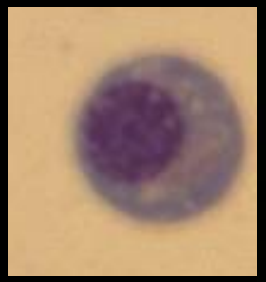
- Serum: β2m, albumin, LDH
- Conventional cytogenetic abnormality
- FISH: <u>on identified plasma cells</u>

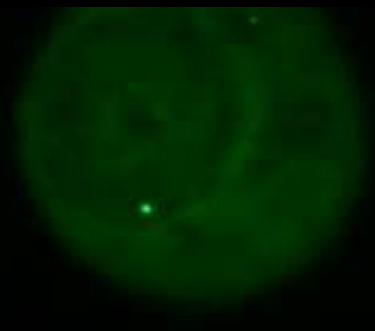
Immuno-FISH

Cell sorting/CD138

GIEMSA + FISH







What risk factors?

FISH

At least : t(4;14)
del(17p)
t(14;16)

Others: 1q, 1p, 8p, 12p, 16q, 22q, hyperdiploidy

What risk factors?

ISS

Based on β2m and albumin levels

Built before novel drug era

Still valid with current approaches?

Method used for measurement should be standard.

Although extremely convenient requires incorporation of additional myeloma-specific features

What risk factors?

Durie-Salmon Staging System

- A system to determine tumor mass
- Still remains a means to measure tumor mass
- Could be replaced by CRAB criteria for diagnosis
- Useful for trial analyses – Stage I versus II/III

What risk factors?

Imaging

- Number of bone lytic lesions, per DS system, is not considered of any prognostic significance.

- Limited series showing prognostic value of MRI

- Might be useful for response evaluation

- Requires further validation studies

Genomics

Gene expression profiling (GEP)

- Two large studies showed prognostic value
- Two different sets of 17 and 15 genes
- Pb: feasibility in multicenter setting

Genomics

SNP/CGH array

- No large series
- Place vs FISH?
- SNP analyses on constitutional DNA

To decide treatment?

Allo-transplants

- For high-risk patients? Or for low-risk?
- Frontline? Or at 1st relapse?

Novel drugs in t(4;14)?

To decide treatment?

Maintenance

- Current level of evidence does not provide direction in deciding if a specific group of patients will benefit from maintenance therapy

Is risk stratification specific for specific treatment

- The risk stratification should be a global stratification, and not stratification for old versus new therapy or risk stratification for particular one treatment.

What other risk factors?

LDH
IgA
extramedullary disease
renal failure
High serum free light chain and κ/λ ratio,
Plasmablastic disease
Plasma cell leukemia

What risk factors?

If a patient already has an identified high risk feature at diagnosis, then there is no need to look for the same feature again.

LDH, IgA, extramedullary disease, renal failure, high serum free light chain and kappa/lambda ratio, plasmablastic disease, and plasma cell leukemia