Update on MDS

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January 14, 2011
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Outline

-Discuss my approach to work-up and treatment considerations for patients with MDS

-For each treatment consideration discuss updates/most recent findings

-Questions

Work-up for MDS

- In addition to standard cytogenetics and FISH for common chromosomal abnormalities, new molecular markers are being identified to further prognosticate MDS patients.
- Additional studies are underway to understand the implications of these mutant genes on clinical course of MDS and survival.
- While testing for these mutations is not standard at this time, expect at OHSU and other facilities testing will become available.

Gene mutated	Frequency	Impact of Mutation
TET2	21%	**Improved overall survival***
ASXL1	14%	**poorer overall survival***
RUNX1	9%	Lower platelet count, higher blast percentage, **poorer overall survival***
TP53	8%	Lower platelet count, higher blast percentage, **poorer overall survival***
NRAS	<5%	Lower platelet count, higher blast percentage,
CBL	<5%	higher blast percentage,
ETV6	<5%	**poorer overall survival***
EZH2	<5%	**poorer overall survival***

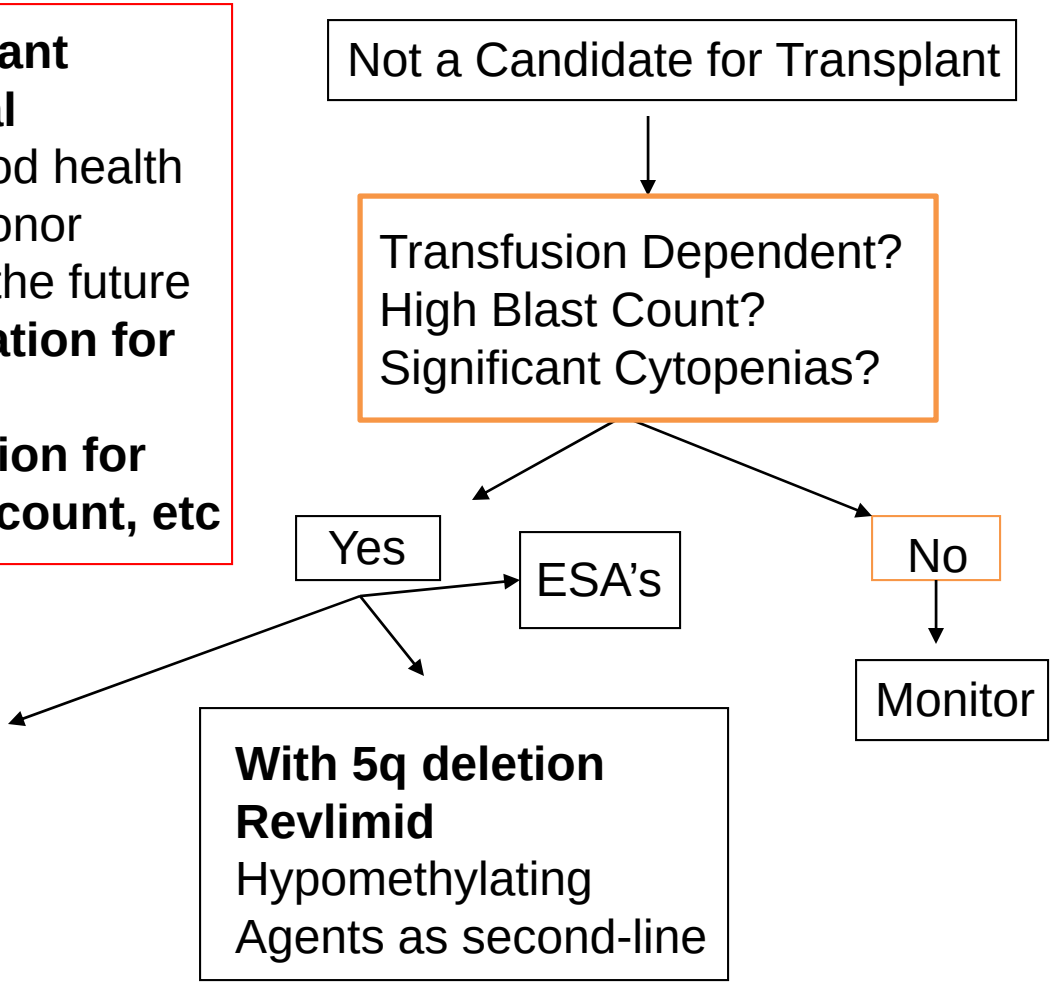
* Independent of IPSS

Treatment Approach for MDS

- Curative options are available for this disease through stem cell transplantation
  - More studies support use of stem cell transplantation in MDS to enhance overall survival
- Active agents against the MDS clone exist for optimization of marrow function, prolongation of development to leukemia, and prolongation of survival
- All patients with MDS warrant an aggressive treatment approach to MDS as long as functional status is preserved.

My Approach to Patients with MDS

Candidate for Stem Cell Transplant
-Age <60 should be early referral
-Age **up to age 75** in relatively good health
-Low risk disease-evaluation for donor
Options for potential transplant in the future
-**High risk disease-urgent evaluation for Transplant**
-**Secondary MDS-urgent evaluation for Transplant irrespective of blast count, etc**



Without 5q deletion
5-azacitidine
-Dose 75mg/m^2 X 7 days
-Plan for 4-6 cycles
Decitabine (20mg/m^2)
-high blast count
-significant symptoms (Sweet's)
-CMML
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Stem Cell Transplant for MDS

- Only curative therapy for MDS
- With reduced intensity regimens this treatment an option for patients up to age 75
- More data is coming out that transplant offers significant survival benefit compared to supportive care alone as well as best treatment with hypomethylating agents.

Transplant Vs. Supportive Care

- 126 patients aged 60-77 were studied. All were higher risk MDS patients. Half of the patients had progressed to AML before transplant as well. Median blast count at tx was 12%.
- Transplant conditioning included one of several reduced intensity (n=79) or more conventional intensity (n=47) regimens and pts transplanted from related (n=50) or unrelated (n=76) donors.
- The outcome after HCT was compared to outcome with BSC only in a matched pair group from the Düsseldorf registry. Matching criteria were age, gender, marrow blast count, FAB and IPSS category.
- **With a median follow-up of 60 months from MDS diagnosis the 5-year overall survival (OS) rate was 45% for the HCT and 25% for the BSC cohort (p=0.008).**
- **In this higher risk MDS population, survival was superior in the transplanted population versus basic supportive care.**
- **This year at ASH the group compared transplanted population with another group treated with 5-Aza.**

Transplant vs. 5-Azacytidine

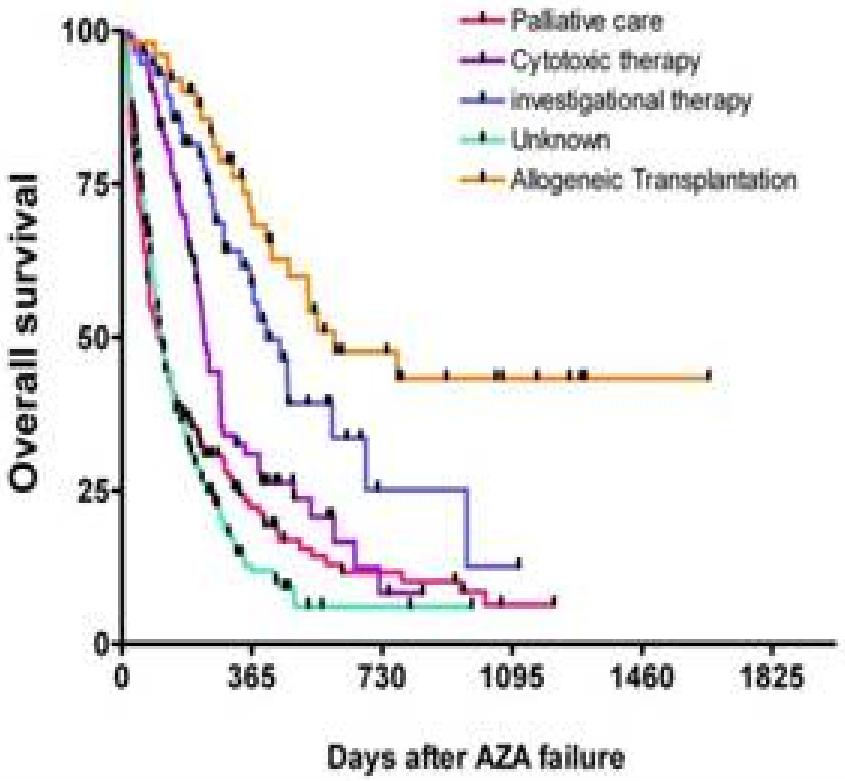
- Same transplant population now compared to patients from the French 5-Aza patient registry
- Matched for age, gender, prior induction chemo, time from diagnosis to therapy, disease stage, cytogenetics. They were well-matched except for age (5-aza median 67 vs. 64). Transplant patients also had higher ECOG score prior to therapy
- Estimated 3-year overall survival was 37% for transplant and 7% for 5-aza groups.
- Multivariate cox regression analysis found ECOG score, disease stage, cytogenetics and type of treatment ($p=0.003$) associated with survival.
- Retrospective analysis suggests a meaningful survival benefit compared to 5-aza in older patients with high-risk MDS, even in the 7^{th} decade of life.

Failure of Hypomethylating Agents

- Numerous studies show that patients that fail hypomethylating agents, either after an initial response or primary refractory patients, have a poor overall outcome, with median survival typically <6 months.
- Study presented at ASH by Prebet et al looked at outcomes of 565 MDS patients after 5-AZA failure.
- Median overall survival of the group was 6 months, with 2-year probability of survival 15%
- Patients who were treated with investigational therapies had median OS of 13.2 months vs. supportive care alone with median OS of 3.3 months.
- Patients transplanted had the best outcomes, with median OS 18.3 months .

Failure of Hypomethylating Agents

Figure 1



Type of salvage	N=	Response rate*	Median OS
Unknown (UNK)	215	NA	3.6 months
Palliative care (PC)	160	NA	3.3 months
Cytotoxic therapy (CT)	84	1/25 and 5/33**	7.6 months
Investigational therapy (IT)	56	4/39	13.2 months
Allogeneic Transplantation (ASCT)	50	17/25	18.3 months

This large study validates what others have shown in smaller studies-patients who fail standard therapies with hypomethylating agents have poor outcomes with supportive care alone.

Best outcomes in this group were in those transplanted.

When to Transplant Patients?

- One has to compare the anticipated problems and survival from the MDS to the risk of transplant to find the right time to transplant patients.
- Lower risk patients-typically do not benefit from early transplant (given better outcome with MDS).
- However, higher risk patients benefit from early transplant given the risk of death from MDS
- This studied by group in Seattle

Survival of MDS Patients Receiving Transplant vs. No Transplant and Risk of MDS

High Risk patients Benefit from early transplant

Low Risk Benefit from Waiting on Transplant

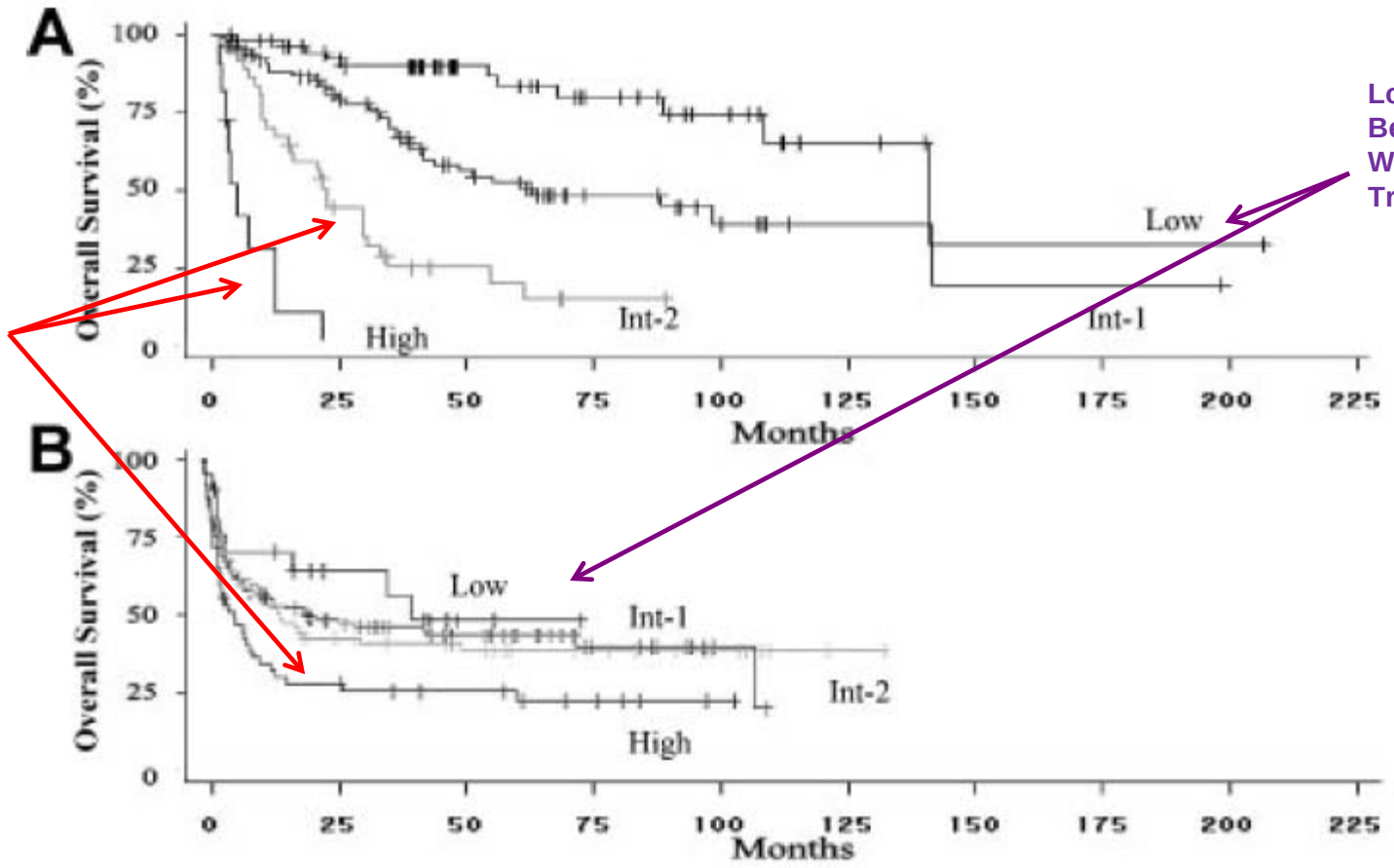


Figure 2. Overall survival of patients included in the analysis. (A) Overall survival of the International MDS Risk Assessment Workshop patients who did not undergo stem cell transplantation, stratified by IPSS score at the time of diagnosis ($P < .001$ for differences in risk groups). (B) Overall survival of the IBMTR/FHCRC bone marrow transplantation cohort of patients, stratified by IPSS risk score at the time of transplantation ($P < .001$ for differences in risk groups).

Goals of Transplantation for MDS-Disease Control with Minimal Toxicity

Pretransplant strategies		*Transplantation*		*Posttransplant strategies*
1. To improve remissions takes: • Hypomethylating agents: - alone - in combinations with HDACs • Induction shortly followed by RIC-conditioning (FLAMSA) • Clofarabine +/- ARA-C **2. Induction of cytogeneic remission:** • Lenalidomide (5q abnormalities) • Hypomethylating agents (monosomy 7)	→ → → → →	Allogeneic stem cell transplantation with toxicity or dose-reduced regimen (according to age and comorbidities)	→ → → →	**1. To prevent relapse:** • Adoptive immunotherapy with preemptive donor lymphocyte infusion • Vaccination therapy or CTLs against tumor-specific antigens • Maintenance therapy - alone - with DLI - with HDACs • Maintenance therapy with lenalidomide

From ASH Education Book 2009

Stem Cell Transplant for MDS

- As transplant strategies improve, transplant becomes a higher priority treatment for MDS patients
- Transplant referrals are appropriate early in diagnosis, even if transplant is not imminent
- Comorbidities impact outcomes, but with reduced intensity regimens this is less important
- Age not always the key feature
- Higher blast count disease increases the risk for relapse-pretransplant therapies important
- Higher age patients likely to require unrelated donors-this is OK and may be better in reducing relapse
- MEDICARE IS NOW COVERING TRANSPLANT FOR MDS!!!

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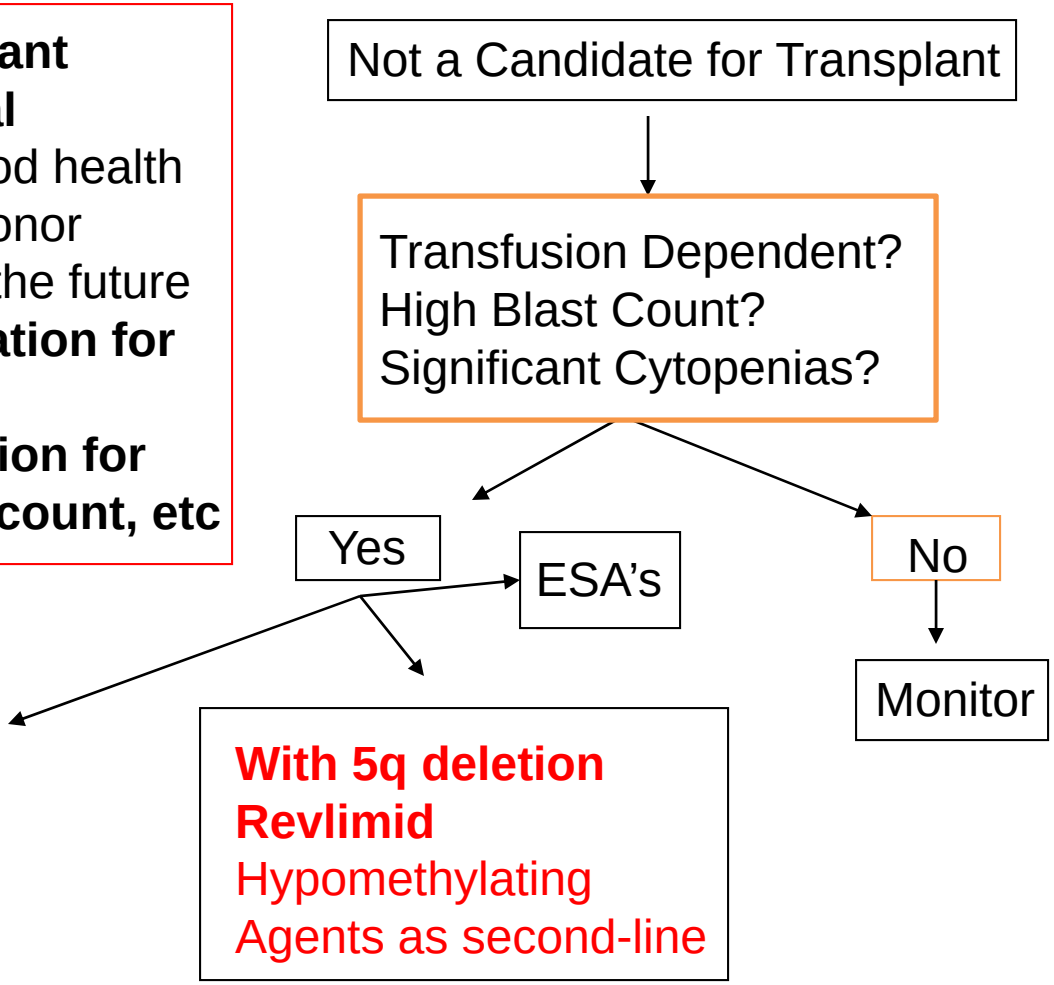

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Revlimid in MDS

- Very effective for 5q deletion MDS
  - Must watch for significant neutropenia and thrombocytopenia with this agent
  - Erythroid responses can be profound and long-lasting
  - Overall well-tolerated side-effects
- For non-5q deletion MDS, small studies show some efficacy. Additional studies from this ASH show real benefit in certain patient populations

Revlimid for MDS with 5q del

- Loss of ribosomal gene RPS14 implicated in 5q- syndrome
- Lenalidomide (Revlimid) is FDA approved for MDS with 5q-. Very specific activity of this drug in 5q- cells, with 70+% of patients responding to this agent (even those with other abnormalities).
- The field of ribosomal dysregulation in defective erythropoiesis is expanding, and there is growing consideration for use of lenalidomide in inherited disorders of red cell production (like Diamond-Blackfan Anemia).

Revlimid for MDS without 5q del

- Activity in MDS without 5q deletion and a treatment consideration for patients.
- Responses take longer to achieve and are not as prolonged as responses in 5q deletion.
- Study at ASH by Sibon et al. looked at 31 low risk patients treated with lenalidomide after failure of ESAs
- 20/31 maintained ESA treatment with lenalidomide
- Overall erythroid response rate 42%. Of those transfusion dependent patients, 42% became transfusion independent, median 12 months response
- For those patients that developed neutropenia and/or thrombocytopenia, their chance of response was lower and response time shorter.
- Revlimid continues to have a place for management of non-5q deletion patients with MDS.

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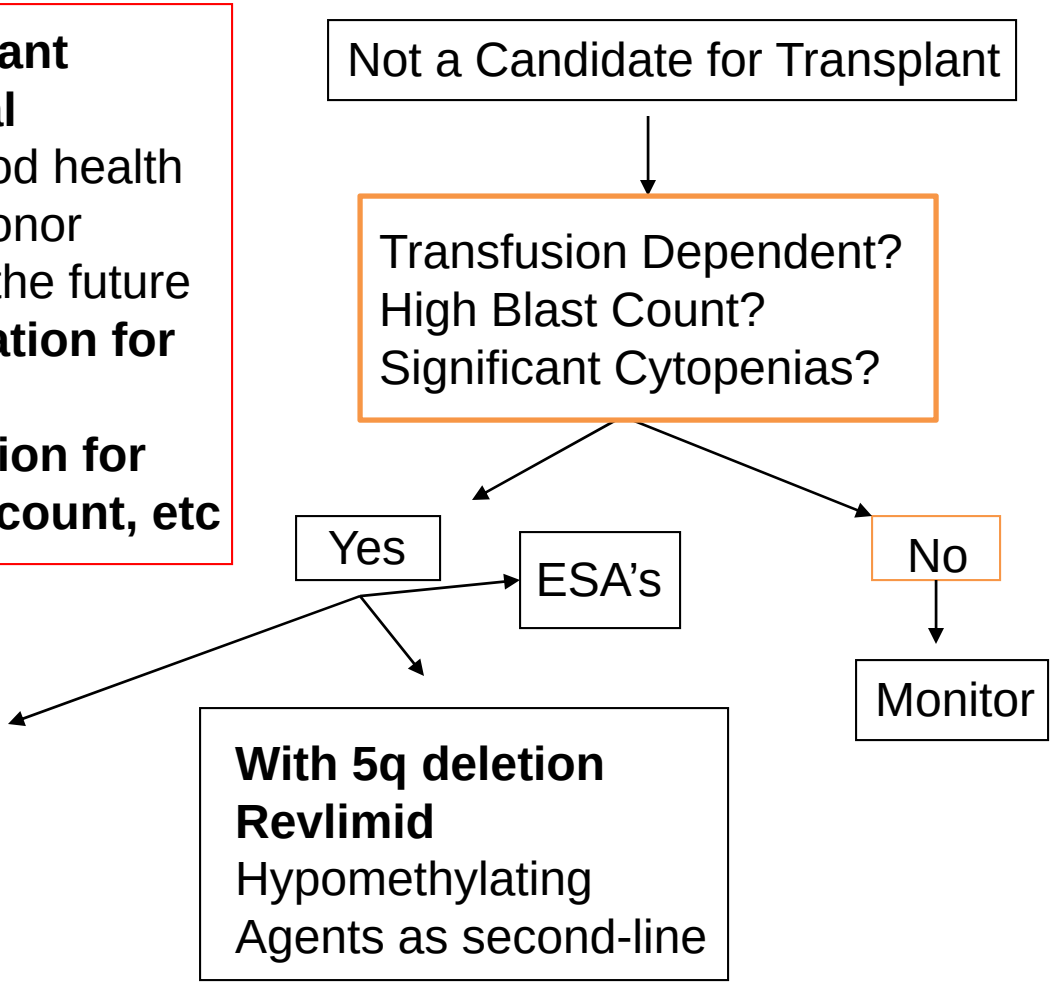

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5-Azacytidine

- Only agent shown to have survival advantage in MDS
- Must give up to 6 cycles to capture all responders, can add ESAs to boost response in partial responders
- Continue to see that activity in responders is prolonged when treatment is continued on a maintenance program
- Can be used as a bridge to transplant, post-transplant to prevent relapse or in post-transplant relapses
- Activity in AML as well-major phase 3 trial compared to standard care included those with RAEB-t (technically leukemia by WHO standards) and these subjects had response and significant survival advantage (24.5 months compared to 16 months)
- While activity is significant, question remains is how to boost responses and depth of responses in patients-longer treatment course vs. adding other agents in combination?

Prolonged 5-AZA Treatment

- Initial results of a phase II study of 5-Aza given as a 10 day course (50mg/m^2 per day X 10 days) alone and in combination with HDAC inhibitor entinostat for high-risk MDS and AML reported by Prebet et al at ASH.
- The group analyzed outcomes of the whole group as well as specific populations.
- In addition, they have compared results to previous trials of the standard 5 day dosing schedule.
- 150 patients accrued to date. 136 available for analysis. 88 MDS, 5 CMML, 43 AML
- Response rates improved compared to previous trials, but not different between AZA alone vs. AZA + entinostat.
- CR 10%, PR 8%, Trilinage improvement 10%. Additional non-trilineage hematologic improvement in 15%, for total improvement of 43%.
- In addition, cytogenetic responses were studied in this treatment group, with complete cytogenetic responses found in 22% of patients (compared to 7% in previous AZA studies with 7 day course).

Prolonged 5-AZA Treatment

- At this time the response rates are equal to slightly better with the 10 day course compared to 7 day course without significant differences in toxicity.
- Depth of response may be higher with 10 day course-whether this will correlate to improvement in overall survival is not clear at this time
- The outcomes from this trial will need to be followed, and at this time I recommend the standard 7 day schedule.

Decitabine

- Continues to show activity in high-risk MDS, CMML and elderly AML, CR rates in 30% range, cytogenetic responses in 50% range
- Analysis of ADOPT trial showed survival prolonged in cytogenetic responders (627 days vs 318 days), responses at 2-3 months
- Again, length of response is maximized with continued treatment rather than discontinuation after maximal response
- All responders captured by cycle #4, with many responses seen after 2 or 3 cycles
- Utilization of decitabine in high-risk patients or those that you want to proceed to transplant is a very good option.

Combined therapies-is more better?

- Histone deacetylase inhibitors are the agents most frequently added to the hypomethylating agents
- Responses seem to be brisker with the combination?
- Higher risk of toxicity?
- Do we capture patients that wouldn't respond to hypomethylating agents alone? I have not been impressed that this is true.

Additional therapies for MDS

- Antithymocyte globulin for lower risk MDS patients has shown some benefit. The typical group that responds includes young patients (<50), low risk, HLA-DR15+. In most studies horse ATG is used.
- Trial looking at rabbit ATG for MDS reported at ASH
- 24 patients treated, 21 evaluable, with 43% response rates. Median time to response 75 days, median response time 7.2 months, with a couple of prolonged responses.
- Immune suppression still has a role for treatment of certain populations of MDS patients.

Additional therapies for MDS

- **Clofarabine**: most promising agent for MDS.
- Phase II study of oral clofarabine in patients who had failed hypomethylating agents (Sekeres et al.) presented at ASH.
- Oral dosing X 5 days every 28 days. High-risk patient population on study, 16 evaluable.
- ORR 30%, with the majority of responses being marrow CR with or without hematologic improvement. Best response seen after 2 cycles.
- This study is enrolling more patients to further characterize best dose
- Another trial that shows the activity of clofarabine in MDS, and this is the most promising agent to treat those who have failed hypomethylating agents.

Additional therapies for MDS

- **Ezatiostat**, an oral glutathione S-transferase inhibitor, activates Jun kinase, promoting the growth and maturation of hematopoietic progenitors while inducing apoptosis in leukemic blasts. Raza et al reported their ongoing study
- 60 IPSS Low-Risk and Int-1 patients studied.
- The overall HI-E rate was 22% (13/60). The median duration of response was 34 weeks.
- Eleven of 38 (29%) RBC transfusion-dependent pts had transfusion reductions with 4 pts (11%) achieving transfusion independence
- Promising agent for lower risk MDS patients.

Additional therapies for MDS

- **Erlotinib**: oral small molecule tyrosine kinase inhibitor that inhibits intracellular EGFR tyrosine kinase. Good consideration for patients that have failed hypomethylating agents. This report by Komrokji et al.
- 25 Higher-risk MDS patients enrolled in this study, with dosing 150mg daily X 16 weeks
- The best responses were 3 marrow CR (13.0%), one HI (4.4%), and 6 (26.1%) stable disease, for a combined ORR of 4/23 (17.4%, 95% CI: 5%-39%).
- Well tolerated with diarrhea and rash main toxicities
- This will be studied in larger cohort.

Summary

- The rates of MDS continue to escalate, with a healthy, older patient population being effected by this disease.
- Morbidity and Mortality from MDS is high, so patients deserve the option of aggressive, potentially curative therapy with the goals of also enhancing survival.
- The literature is gathering to support earlier use of stem cell transplantation for MDS.
- We now have support from Medicare for transplant
- Hypomethylating agents remain first line therapy for higher risk patients. They provide enhanced survival, QOL and prolongation of time to leukemic transformation
- However, for those who fail this therapy, poor outcomes arise without aggressive treatment.