MDS Conceptual Framework Identifies Unmet Need for HMA-Unresponsive and Transplant-Ineligible Patients

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BACKGROUND

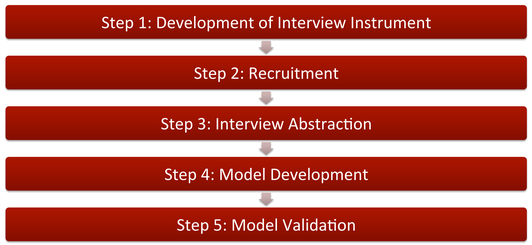
- MDS patient prognosis is grim, with overall survival reported between 4.3 and 5.6 months and 3-year relative survival across all age groups estimated at 45% (inversely related to age at diagnosis).[1,2]
- While hypomethylating agents (HMAs) improve survival and delay disease progression of MDS, most patients either fail to respond to HMA therapy or relapse after initial response.
- Little data exist about diagnostic and treatment decision-making for non-transplantable, higher-risk MDS patients with HMA treatment failure.
- In this analysis, researchers evaluated physicians' approaches to making decisions related to MDS patients':
  - diagnosis,
  - risk classification,
  - progression,
  - and treatment.

METHODS

Overview

- Semistructured interviews were conducted with 9 US-based clinical MDS experts (Steps 1-3)
- A conceptual model was developed based on interview responses that described current MDS management decision-making options and pathways (Steps 4-5)

Figure 1. Interview and Model Development Process



Step 1: Development of Interview Instrument

- A search was conducted in PubMed for publications containing MDS data
- Through review of the published literature and based on expert opinion, parameters that could impact MDS treatment decisions were identified:
  - Risk classification
  - Age
  - Performance status
  - Eligibility for allogeneic hematopoietic cell transplant (HCT)
  - Toxicity profile of available treatment
  - Disease progression that caused changes in MDS-related treatment
- Interview questions were developed based on findings (Table 1)

Table 1. Subset of Semistructured Interview Questions

A. Practice Setting		B. Diagnosis, Treatment, and management	
A1	What is your medical specialty?	B1	Would you describe very briefly the process you go through when you diagnose a new patient that you suspect has MDS?
A2	How many years have you practiced in (that/those) specialty?	B2	How do you determine your management approach for patients after they are diagnosed?
A3	About how many MDS patients do you see in a typical year?	B3	How do you determine whether a patient's MDS is progressing?
A4	(About) what percentage of your MDS patients are newly diagnosed when they first see you?	B4	Please describe how you treat patients that are determined to be "high risk," and by treatment I mean supportive care, transfusions, EPO, chemotherapy?
A5	(About) what percentage of your MDS patients would you consider to be "high risk" when they first see you?	B5	After you have tried chemotherapy with an HMA, what additional treatment options do you consider?

Step 2: Recruitment

- Clinicians were invited to participate in the interview based on:
  - Number of years in practice
  - Type of practice
  - Frequency of treating MDS patients
  - MDS disease severity in patient population
- Variation across these criteria was sought when selecting providers to interview

Step 3: Interview Abstraction

- During each interview, while a researcher asked survey questions, a second researcher transcribed responses in a summary format
- Abstraction tables were created based on providers' responses

Step 4: Model Development

- Areas of consensus and variation between responders were identified
- A symbolic representation of the treatment model pathway was created

Step 5: Model Validation

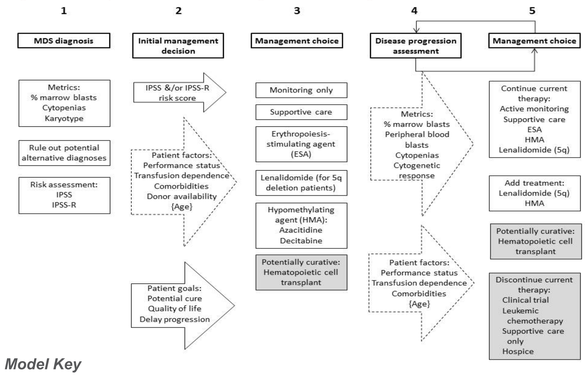
- Five experts reviewed the model structure and concepts
- A second and final iteration of the model was developed based on the experts' responses

RESULTS

Overview

- Interviews were conducted over a 6-week period (August - September 2013)
- Average interview was 45 minutes in length
- 9 oncology and hematology specialists were interviewed
- We organized each interview around 5 Key Concepts in the MDS treatment process (Figure 1):
  1. MDS Diagnosis
  2. Initial Management Decision
  3. Management Choice
  4. Disease Progression Assessment
  5. Management Choice

Figure 1. Conceptual Model of MDS Diagnosis and Management



Model Key

- Rectangles: Diagnostic and treatment choices (static events)
- Arrows with dotted lines: Decision-making processes; areas of substantial variation based on providers' responses
- Arrows with solid lines: Decision-making processes; areas of agreement across providers
- Arrows that connect stages 4 and 5: MDS patients follow a cycle of management-assessment-reassessment until they reach one of two end points (shaded in gray):
  - Potential cure following HCT, or
  - Treatment fails

Table 2. Profile of Providers Interviewed

Parameter	Response
Practice setting:	
Academic medical center	7
Community-based oncology practices	2
Number of years in practice:	
Average	15 years
Range	8-40 years
Patient demographics:	
Number of unique MDS patients (per year)	100-200 (8 providers); 20-30 (1 community-based provider)
MDS severity:	
Academic medical center	50-80% (6 providers); 30% (1 provider) "higher risk" patients
Community-based oncology practices	75-80% (2 providers) "lower risk" patients
MDS diagnosis	
Academic medical center	50-80% patients diagnosed by another provider
Community-based oncology practices	"Almost all" patients received initial diagnosis by provider

MDS Diagnosis

- Providers generally agreed about the methods to use when diagnosing MDS
  - Most (N=8) providers always calculate a risk score for treatment-naïve MDS patients, using either IPSS alone, IPSS-R alone, or IPSS and IPSS-R in combination
  - Bone marrow biopsy, karyotyping, and evaluation of number of cytopenias were also stated as being used, although less frequently

Initial Management Decision

- Factors in providers' decision-making process included:
  - Patients' IPSS-R risk score (which take into account peripheral blood, bone marrow, and cytogenetic indicators), age, and performance status
  - Transfusion dependence
  - Availability of suitable bone marrow donor

Management Choice

- Supportive care is the initial treatment option for patients with low IPSS-R scores (≤3)
- Transplantation was providers' preferred treatment choice for newly-diagnosed, young and otherwise healthy high-risk patients
- In line with findings from published literature, providers:
  - Reported that only HMAs and lenalidomide were proven to delay MDS progression and/or improve survival in patients who are not eligible for transplant
  - Expressed belief that HMAs are effective for a period of time, but eventually fail

Disease Progression Assessment

- A conclusive measurement of disease progression is attained through measuring patients' complete blood counts (CBC) on a periodic basis
- Physicians may also use the following tests as indicators, however they are not necessarily as conclusive as CBC:
  - IPSS and IPSS-R (for treatment-naïve patients)
  - Bone marrow biopsy
  - Transfusion requirements
  - Cytogenetic response

Management Choice

- MDS treatment methods change when patients develop progressive or new cytopenias, symptoms worsen, and/or a high-risk disease determination is made
- Clinical trials, chemotherapy, and supportive care are the only second-line options for treatment failure
- Due to limited effective 2nd-line treatments or management approaches, providers may to continue to treat patients with HMAs "just to do something"

CONCLUSIONS

- We found variation among provider responses relating to:
  - assessment of disease progression,
  - definition of treatment failure,
  - decision to stop 1st-line treatment,
  - and treatment of intermediate-risk patients.
- There was consensus among providers that all patients receiving HMAs will eventually progress, thus the lack of 2nd line options after HMA failure is an issue of profound importance to providers and patients.
- Alternative treatment options to address the unmet medical needs of MDS patients who have failed HMAs would greatly impact MDS patients and assist providers in the management of these patients.

REFERENCES

1. Prébet *Journal of Clinical Oncology* 2011; 2. Jabbour *Cancer* 2010.

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