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Risk stratification, treatment selection, and transplant eligibility in multiple myeloma: a qualitative study of the perspectives and self-reported practices of oncologists

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ABSTRACT

Background Since the early 2000s, treatment options for multiple myeloma have rapidly expanded, adding significant complexity to the management of this disease. To our knowledge, no systematic qualitative research on clinical decision-making in multiple myeloma has been published. We sought to characterize how physicians view and implement guidelines and incorporate novel approaches into patient care.

Methods We designed a semi-structured qualitative interview guide informed by literature review and an expert advisory panel. We conducted 60-minute interviews with a diverse sample of oncology physicians in the southeast United States. We used a constant comparative method to code and analyze interview transcripts. The research team and advisory panel discussed and validated emergent themes.

Results Participants were 13 oncologists representing 5 academic and 4 community practices. Academic physicians reported using formal risk-stratification schemas; community physicians typically did not. Physicians also described differences in eligibility criteria for transplantation; community physicians emphasized distance, social support, and psychosocial capacity in making decisions about transplantation referral; the academic physicians reported using more specific clinical criteria. All physicians reported using a maintenance strategy both for post-transplant and for transplant-ineligible patients; however, determining the timing of maintenance therapy initiation and the response were reported as challenging, as was recognition or definition of relapse, especially in terms of when treatment re-initiation is indicated.

Conclusions Practices reported by both academic and community physicians suggest opportunities for interventions to improve patient care and outcomes through optimal multiple myeloma management and therapy selection. Community physicians in particular might benefit from targeted education interventions about risk stratification, transplant eligibility, and novel therapies.

Key Words Multiple myeloma, qualitative research, treatment decision-making, risk stratification

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INTRODUCTION

The treatment of multiple myeloma (MM) has evolved considerably since the early 2000s, especially with the introduction of immune-modulating drugs and proteasome inhibitors, and more recently, novel targeted therapies[1]. Those agents have markedly improved treatment response rates and overall survival[2–10]. Furthermore, testing techniques have also improved with the advent of serum free light-chain assays and "tumour profiling" techniques such as fluorescence *in situ* hybridization and "minimal residual disease" detection assays[11–13]. Those advances have ushered in a new era of risk stratification in MM management[14,15]. Transplantation-related mortality has also declined, such that older and more frail patients are increasingly offered autologous stem-cell transplantation (SCT)[16].

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The advances are welcome, but they have occurred relatively quickly, and they add significant complexity to treatment decision-making. The rapid pace of the advancements could make it challenging for busy oncologists to keep up with changing paradigms, particularly with respect to applying new evidence to patient care. Evidence-based guidelines are particularly important in helping to translate cutting-edge advances into practice and to standardize therapeutic approaches across diverse practice settings[17]. Notably, new guidelines from the International Myeloma Working Group and the U.S. National Comprehensive Cancer Network (NCCN) recommend the use of risk assessment and risk-adapted treatment of MM[14,15,18–20]. However, population- and practice-level data about initial MM treatment patterns point to considerable variability in practice[21,22]. The underlying drivers of that variation remain poorly understood.

It is important to understand how physicians view and implement guidelines and incorporate novel approaches into patient care. Although several qualitative studies have examined the strategies that physicians use to make treatment decisions in the face of competing priorities[23–25], we are not aware of any systematic qualitative research on clinical decision-making with respect to recent advances in MM. To characterize how physicians view and implement guidelines and incorporate novel approaches into practice, we therefore conducted an in-depth qualitative assessment of community and academic practice in the southeast United States.

METHODS

Design

We convened an expert advisory panel to design the overall study approach. The panel included an academic MM specialist (SAT), a MM and SCT specialist (CG), a general hematologic oncologist (TWL), a qualitative researcher (AH), a research organization program planner (PS), and an oncologist and palliative care physician with experience in qualitative research, clinical trials, and outcomes research (APA). A literature review informed the panel's approach, with specific attention to and discussion of recent MM treatment guidelines from the International Myeloma Working Group and the NCCN. We developed a qualitative semi-structured interview protocol comprising open-ended questions to guide interviews focused on the stated rationales of physicians for treatment selections in the first-line and relapsed or refractory settings, use of risk stratification and risk-adapted therapy, criteria for transplant eligibility, the role of non-physician clinicians in MM care, strategies for managing side effects and treatment-related toxicities, methods for educating patients, and use of newer therapeutic agents.

Sample

We prospectively identified a geographically convenient sample of hematology oncology clinics in the southeast United States (North Carolina, South Carolina, and Virginia). Clinics were chosen to represent a range of academic, academically-affiliated, large private-practice, and independent private-practice settings. Investigators TWL, CG, and SAT personally invited (by e-mail and telephone) 31 physicians and non-physician clinicians to participate. The clinicians represented 5 different academic and 4 community practices. To ensure anonymity, we have not identified the names or characteristics of the individual practices. Participants were offered an honorarium in appreciation of their time. The Duke University Institutional Review Board reviewed and approved the conduct of the study, and the research team gathered signed informed consent from all participants before interview. Of the 20 clinicians who enrolled and completed interviews, 13 were physicians, 1 was a physician assistant, and 6 were nurses or nurse practitioners. Here, we present the analysis of the physician data.

Data Collection

We conducted semi-structured telephone (n = 7) and in-person (n = 6) interviews; all were completed by February 2014. Interviews were scheduled for 60 minutes and were conducted by 2 trained qualitative researchers (AH, WT). Interviews were audio recorded and transcribed verbatim by an independent transcriptionist.

Qualitative Data Analysis

Qualitative analysis encompasses data interpretation and generation of themes and hypotheses in an ongoing, iterative process[26]. We imported transcripts into the NVivo 10 Qualitative Analysis Software (QSR International, Doncaster, Australia) and used a process of constant comparison to structure our analysis of participant responses across and within interviews[27]. Analysts reviewed and coded all transcripts into anticipated and *de novo* descriptive codes (or "nodes") that were tagged to sections of text and then tested, refined, and compared across interviews[26]. Within each descriptive node, analysts identified potential themes of interest and relevance and merged concepts or nodes into abstract categories or major themes until thematic saturation was achieved (a qualitative hallmark of an adequate sample size). Indicators of themes included words, phrases, or segments of text that were used in a similar fashion and denoted a particular idea or concept. Themes were compared in framework matrices within and across transcripts for consistency or variation in meaning, and also across community and academic attributes. After the initial coding, the research panel reviewed the interim findings and resolved any differences in interpretation through consensus discussion.

RESULTS

Participant Characteristics

All participants were clinicians who actively manage patients with MM and who practice hematology oncology in academic or community settings in North Carolina, South Carolina, and Virginia (Table I).

Risk Stratification and Induction Therapy

All the academic physicians reported using risk stratification before initiating treatment in newly diagnosed patients. Interviewees cited a wide range of risk stratification strategies, although academic physicians identified

TABLE I Participant characteristics

Characteristic	Value (*n*)
Practice location	
North Carolina	17
South Carolina	2
Virginia	1
Designation	
Physician	13
Physician assistant	1
Nurse practitioner	5
Registered nurse	1
Practice setting	
Academic	13
Community	7
Sex	
Men	10
Women	10

cytogenetic testing as the most valuable risk assessment tool, followed by the formal International Myeloma Working Group or NCCN risk stratification criteria[22]. Only 1 community physician reported using risk stratification in his practice—indeed, the predominant approach to determining transplantation referral and induction therapy for newly diagnosed patients in the community was informal. For instance, when asked about the use of risk stratification, one community physician responded, "I don't. I use it in my mind, thumbs up, thumbs down. I don't look up the ... hemoglobin and the calcium and this other stuff."

When asked to describe the implications of risk stratification for the kinds of induction regimens to recommend for patients, academic and community physicians both invariably reported that the outcomes of risk stratification made little difference to their initial therapy selection. Overall, academic and community physicians generally reported using the same few triplet regimens for all patients in the first-line setting.

> We'll look at their risk factors, including cytogenetics and other things. Having said that, I think the majority of them are going to end up on a bortezomib-containing regimen either way.
>
> — Academic physician

> I mean most often—so we would look at the genetics and, if they have high-risk genetics, sometimes we treat them with a slightly different regimen, but most patients we treat with the same approach.
>
> — Academic physician

> Well, I usually use the same thing for first line, which is bortezomib with cyclophosphamide and dexamethasone, and then, very rarely, I give [lenalidomide] first-line.
>
> — Community physician

Academic physicians reported using 2 regimens as primary therapy: lenalidomide–bortezomib–dexamethasone and cyclophosphamide–bortezomib–dexamethasone. None of the participants reported either using or seeing newer agents (that is, carfilzomib) in the frontline setting or the use of any 4-drug regimens upfront.

Transplant Eligibility

With one exception, all physicians viewed SCT as central to the treatment of patients with MM and described referring all eligible patients for transplantation. They all acknowledged the important role of transplantation and of MM specialists in deciding patient eligibility for transplantation. Although referring oncologists (both academic and community) reported having transplant eligibility criteria in mind when referring patients to transplant specialists, physicians predominantly reported that they deferred to the expertise of transplantation specialists in determining transplant eligibility. However, differences were evident between the broad transplant eligibility criteria used by community physicians and the more specific criteria used by academic physicians and transplantation specialists, which they described as informing their decisions about whether to refer patients to a transplantation specialist (Table II).

Transplantation specialists tended to report more-specific, objective criteria; academic and community oncologists more often indicated taking into account patient and social criteria (logistics and sense of patient tolerability, for instance). Compared with the academic physicians, community physicians placed more emphasis on psychosocial factors and used lower age cut-offs.

> Rarely, it's the disease that's preventing them from going to transplant in terms of they're just too debilitated, too poor a performance status. It's more likely to be some sort of a psychosocial factor honestly.
>
> —Community oncologist

Regardless of clinical eligibility, physicians did not refer patients for transplantation if the patients preferred to forgo it or if the physician felt that the patient lacked social support or psychosocial capacity.

Maintenance Therapy

All but 2 physicians across the academic and community settings reported using maintenance therapy for both post-transplant and transplant-ineligible patients. The duration of maintenance therapy reported by this group varied from 2–5 years to indefinitely, and the most frequently reported maintenance strategy was to use reduced doses of current medications, especially lenalidomide. Physicians more often reported using lenalidomide than bortezomib as the maintenance treatment of choice, typically in lower doses than during induction or first-line treatment (for transplant-ineligible patients). Physicians preferred lenalidomide because they associated it with ease of administration, less toxicity (compared with the other options), and supportive clinical data, particularly in the post-transplant setting.

TABLE II Transplantation criteria by provider type

Provider type	Criteria
Transplant specialist	■ *Therapeutic response* Confirmed therapeutic response to induction therapy (International Myeloma Working Group partial response or better)
	■ *Performance status* Reported use of Eastern Cooperative Oncology Group ≤2, Karnofsky ≥70
	■ *Plasma cell percentage* ≤20% Plasma cells in marrow; ≥20% if partial response
	■ Compliance with transplant requirements
Academic	■ Genetics, plus "full work-up"
	■ <65 Years of age; active, functional; good response to therapy
	■ Most patients referred for transplantation evaluation after partial response
Community	■ <70 Years of age
	■ Performance status important ("functional status," "frailty," "able to manage at home")
	■ Organ function, physiologic reserve
	■ Psychosocial situation
	■ Logistics (ability to travel for transplantation procedure)
	■ Cost
	■ Cognitive challenges (inability to fully appreciate implications of treatment)

Physicians generally characterized bortezomib as their second option, reserved for patients who did not tolerate lenalidomide maintenance. One academic physician noted that he would use bortezomib as maintenance therapy specifically for patients with a 17p deletion on cytogenetic evaluation. Two academic physicians reported using thalidomide as maintenance therapy for patients unable to tolerate lenalidomide.

Community physicians tended to follow the recommendations of transplant physicians in their selection of maintenance therapy, but they noted that when they lacked such guidance, it was especially tricky to devise an effective maintenance regimen.

> You don't have a lot of guidance. You kind of have to use your instincts and your experience with previous patients ... so [after initial treatment] I will begin peeling off agents.
>
> — Community oncologist

Recognition of and Treatment at Relapse

Academic and community physicians identified a range of factors that they monitor to determine relapse, including protein levels, serum free light-chain testing, 0.5 g/dL or more monoclonal spike, 10% or greater increase in plasma cells, and appearance of MM complications, including new bone lesions, worsening of existing lesions, or renal insufficiency. All physicians regarded relapse as a subtle phenomenon and viewed relapse identification as clinically challenging despite existing guidelines, particularly with respect to when a change in therapy was warranted.

> What's very hard is if there's subtle changes in the serology. It's very hard.... The experts cannot give me an answer on what the definition of relapse disease is. So how am I possibly supposed to know it when the people that only see mm in their entire lives don't even know it. So I don't know.
>
> — Community oncologist

> Before I commit this person to more intensive therapy—you know, let's make sure that this is truly [relapse].... Because we know sometimes there can be fluctuations, and it's like sometimes you can pick up a different clone.
>
> — Academic oncologist

Although all physicians acknowledged the rapid expansion of treatment options for patients in both the first-line and relapsed settings, and sought balance between maintaining quality of life and treating patients with the most aggressive therapy tolerated, key differences in strategies for the treatment of relapsed MM were evident. Academic oncologists talked more than community physicians about using "aggressive" treatment in the relapsed setting, identified clinical trials as the optimal path for patients after relapse, and more frequently used newer agents after relapse. Compared with community physicians, academic physicians also reported using a wider range of agents or combinations thereof in the relapsed setting; they appeared more comfortable using newer agents. The community physicians typically reserved newer agents for "last ditch" efforts (Table III).

DISCUSSION

The management of patients with MM is irrefutably challenging for all oncologists. It is especially challenging for physicians in community settings, for whom myeloma may well represent only a small proportion of their total patient population. As new therapeutic combinations and molecular profiling techniques expand, the challenges

TABLE III Reported trends in post-relapse treatments (unprompted regimen mentions during interviews)

Agent or combination	Setting	
	Academic	Community
CyBorD	X	X
Lenalidomide, carfilzomib, dexamethasone	X	
Cyclophosphamide, carfilzomib, dexamethasone	X	
Carfilzomib, pomalidomide, dexamethasone	X	X
VD-PACE	X	
Melphalan	X	
Pomalidomide and dexamethasone	X	
Lenalidomide and dexamethasone	X	X
Carfilzomib monotherapy	X	X
Bortezomib and dexamethasone	X	
Carfilzomib (monotherapy or combination unspecified)	X	X
Thalidomide or DCEP	X	

CyBorD = cyclophosphamide, bortezomib, dexamethasone; VD-PACE = bortezomib, dexamethasone plus platinum agent, doxorubicin, cyclophosphamide, etoposide; DCEP = dexamethasone, cyclophosphamide, etoposide and cisplatin.

can only intensify. The recent and rapid growth in available and effective therapies, even in relapsed disease settings, is unprecedented, but it complicates clinical decision-making and makes keeping up with the latest advances difficult. In our qualitative in-practice study of MM treatment decision-making amid rapid advances in available therapies, we found differences in how academic and community physicians address risk stratification, assessment of transplant eligibility, assessment of treatment response, and maintenance therapy in clinical practice. We believe that attention to these areas of practice through education and resource provision can support oncologists and improve their confidence in making treatment decisions informed by risk stratification. A brief discussion of each key finding follows.

Risk Stratification

When planning initial therapy, physicians must consider a range of factors, such as disease staging, comorbid conditions, performance status, renal function, transplant eligibility, and assessment of cytogenetic and fluorescence *in situ* hybridization abnormalities[19]. Several studies point to biologic factors that influence risk and prognosis in MM and that have a bearing on choice of initial therapy. To improve clinical outcomes, risk stratification is increasingly considered an important strategy in treatment determination[14,15,18]. However, although academic physicians reported using risk stratification as part of their clinical routine, community physicians typically did not. And although physicians reported using induction regimens that reflected current evidence and contemporary MM practice recommendations[19,20], they largely reported that the outcomes of risk stratification made little difference to their initial therapy selection. Some physicians seem, regardless of patient risk category, to be selecting such regimens for both transplant-eligible and -ineligible patients—a trend that was particularly noticeable among community physicians. Perceptions on the part of community physician of first-line and induction regimens as complex, combined with little guidance about therapy selection, might pose barriers to following a more risk-adapted therapy schema.

Transplant Eligibility

The optimal timing of SCT in the era of novel agents remains a contentious issue, although compared with conventional therapy, SCT has been associated with a survival advantage in randomized controlled trials (improved progression-free survival and overall survival)[7]. Based on current guidelines, early SCT represents a standard of care for eligible patients, and it is widely used in clinical practice. For instance, analysis of the U.S. National Cancer Institute's Patterns of Care studies data has shown that, between 1999 and 2007, SCT increased to 21.7% from 11.1%[21]. The differences in transplant eligibility criteria reported by the physicians in our study have important implications for the timing of referral for transplantation and for the choice of patients who are ever referred for transplantation. Notably, distance, social support, and psychosocial capacity were important recurring factors for community physicians in their decision-making about transplantation referral. However, many of those issues can be successfully addressed with supplemental resources provided through comprehensive transplantation programs. It is thus concerning that some physicians might avoid referring MM patients for SCT because of issues that can readily be addressed. The range of transplant eligibility criteria noted by respondents suggests a need for ongoing education about those criteria and how to identify and address nonclinical factors that might influence a physician's decision to refer a patient for transplantation (for example, distance, cost, and psychosocial capacity).

Maintenance Therapy and Relapse

Two key studies have shown a benefit for lenalidomide maintenance therapy after SCT[9,10], and compared with thalidomide, bortezomib has also shown improved survival when administered as part of a program that included bortezomib maintenance therapy[28]. The current NCCN guidelines recommend all 3 agents as maintenance therapy options[20], although optimal regimens for maintenance therapy continue to be a focus of current research.

Most of the physicians in our study reported using a maintenance strategy for both post-transplant and transplant-ineligible patients, but they noted the challenge of determining the timing of maintenance therapy initiation and the response. Community physicians were particularly concerned about the lack of guidance in this area, a gap that has also been discussed in the wider literature[19]. Similarly, the challenges in recognizing relapse highlight a clear area of educational need, because subsequent therapy depends on timely recognition of relapse. References by our respondents to the inherent difficulties in identifying relapse might reflect misunderstandings about, or low

awareness of, the definition of relapse in the literature. However, it is more likely that participant perspectives on relapse interpretation reflect very tangible challenges in translating subtle criteria into clinical practice, especially when guidelines sometimes conflict.

Limitations

There are limitations to our approach in this study. First, to ensure feasibility and in-person interviews whenever possible, we focused on a geographically constrained area of the southeast United States. Practices in other regions could vary, although the diversity of clinicians and practices represented here provide some insight into potential practice variation. We recruited not only from all the academic practices in the area, but also from many diverse community practices. Second, as is conventional in qualitative research, our sample size is small. However, qualitative analysis does not typically require large sample sizes to yield meaningful insights, and it is not unusual to reach the point of "thematic saturation" (the equivalent of statistical power for this type of research), after 10 or 12 interviews, as happened here[27]. In other words, the seemingly small sample size is not actually small for a qualitative study. Additionally, the intention of qualitative research is not to generate generalizable findings, but rather to yield deep insights drawn from the perspectives of study participants. As such, our findings should inform subsequent, larger studies that can use quantitative methods such as surveys to further explore treatment decision-making in MM.

CONCLUSIONS

We have described several disconnects between published guidelines and self-reported clinical practice in MM treatment. Notably, compared with academic physicians, physicians in community-practice settings made minimal use of formal risk-stratification assessments. In contrast, academic and community physicians both used similar induction regimens for initial treatment regardless of risk stratification. Many participants described difficulty recognizing relapse and knowing how to manage maintenance therapy. Participants cited widely variable criteria for transplant eligibility, which suggests that many eligible patients are not being referred for transplantation, particularly in the community-practice setting.

As treatment for patients with MM continues its rapid evolution, our findings suggest the need for more straightforward guidelines and targeted education about risk-adapted therapy, assessment of relapse, use of maintenance therapy, and transplant eligibility. Interventions in those areas could potentially have a sizeable impact on treatment patterns and quality of care in MM, especially as more new therapies become available. Such efforts might be particularly helpful in the community-practice setting.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SAT has received research funding and honoraria from Celgene and Takeda, and has participated in speaker's bureaus for Celgene and Takeda; CG has received research funding from Celgene and honoraria from Celgene and Millennium, and has participated in speaker's bureaus for Millennium and Celgene; SK and ZMK are both employees of Celgene Corporation; APA is an employee of Flatiron Health, Inc.; TWL has received honoraria from Pfizer, Boehringer Ingelheim, and Flatiron Health, Inc. AH, WT, PS, and SCL declare that they have no conflicts to disclose.

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