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Combination therapy for fit (younger and older) newly diagnosed multiple myeloma patients: Data support carfilzomib, lenalidomide, and dexamethasone independent of cytogenetic risk status

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ABSTRACT

In this invited paper, I was asked to critically review available literature and seek scientific and clinical evidence to argue in support of carfilzomib, lenalidomide, and dexamethasone (KRd) as the new default therapy for fit patients with a new diagnosis of multiple myeloma (MM). When performing the review of existing data and when writing this paper it became clear to me that both KRd and bortezomib, lenalidomide, and dexamethasone (RVd) are both recommended by established, well-respected expert guidelines. Importantly, the actual data behind guidelines supporting KRd and RVd come from phase II studies; thus, the level of scientific evidence behind KRd and RVd is the same. When reviewing efficacy and safety data for both regimens, I conclude that published peer-reviewed KRd original data are well in line with modern treatment goals for newly diagnosed MM patients: rapid, deep, and sustainable treatment effect with limited toxicity. Taken together, available scientific and clinical evidence favors KRd as the new default therapy for fit patients with a new diagnosis of MM. Original data support KRd independent of cytogenetic risk status; indeed, patients with standard-risk disease (which represents 75% of all newly diagnosed MM patients) have the strongest benefit of KRd.

Induction Therapy: Clinical Vignette

A 56-year-old man presents with anemia (hemoglobin: 8.6 g/dL) and lower back pain. A PET/CT scan reveals multiple FDG-avid lytic lesions in the spine, as well as the left humerus. A serum protein electrophoresis is notable for a monoclonal spike in the gamma region measuring 4.1 g/dL and a corresponding serum immunofixation confirms IgG kappa monoclonal protein. Serum free kappa is elevated at 56 mg/dL and the free lambda is 0.43 mg/dL for an elevated kappa/lambda ratio of 130.2. Serum β_2-microglobulin is elevated at 3.8 mg/L and serum albumin is 3.6 g/dL. Serum creatinine and calcium are both within normal limits. Bone marrow biopsy reveals trilineage hematopoiesis with 70% plasma cell infiltration and corresponding FISH/cytogenetic analysis shows no myeloma-specific cytogenetic abnormalities. Patient returns to your clinic after work-up for further management.

Question: What is the optimal induction therapy for a transplant-eligible multiple myeloma patient with normal cytogenetics?

I was given the task of supporting the use of carfilzomib, lenalidomide, and dexamethasone (KRd) as therapy for patients with a new diagnosis of multiple myeloma (MM). I will argue that KRd is well in line with modern treatment goals for MM: rapid, deep, and sustainable treatment effect, with limited toxicity. Based on available data on its efficacy and safety profile in the United States, I would conjecture KRd will replace bortezomib, lenalidomide, and dexamethasone (RVd) as the standard of care for "fit patients" with a new diagnosis of MM [1]. Outside the United States, restricted access (due to costs, regulatory processes, and other reasons) will most probably continue to delay and hinder the use of newer therapies.

I will begin by giving a brief background of the treatment of MM and then review formal data and expert guidelines on treatment options available for patients with newly diagnosed MM. I will not argue that I know better nor pretend that there is one truth and everything else is wrong. Simply, that is not how clinical medicine —or life in general—works. Instead, by outlining facts and caveats, and discussing the data critically, my intent is to let the reader draw his/her own conclusions.

1. The success of modern multiple myeloma therapy

MM has become the poster child of success in hematology–oncology. At the start of the 21st Century in the United States, MM

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Table 1
Three types of support used in making clinical decisions.

Type of support	Sources	Comments
Survival data	Randomized phase III clinical trials	Pros: No ascertainment bias in blinded randomized studies Cons: Larger sample size, longer follow up
Surrogate endpoint data	Single-arm or randomized phase II or phase III clinical trials	Pros: Smaller sample size, shorter follow up Cons: Not precisely measured May introduce ascertainment bias in open-label studies Definitions can vary across studies and over time due to new criteria
Expert guidelines	Based on reasonable belief [4] (such as NCCN guidelines; Memorial Sloan Kettering guidelines; Mayo Clinic guidelines; see Table 3)	Pros: Relies on expert guidance Cons: Opinion-based No standardized rules that apply to all expert guidelines

had an average overall survival (OS) of about 3 years [2]. By 2014, access to better drugs had increased the median OS of patients younger than 50 years to more than 10 years [2]. The US Food and Drug Administration (FDA) approved 14 new drugs for the treatment of cancer in 2015; four of these were for the treatment of MM: panobinostat, daratumumab, elotuzumab, and ixazomib [3]. In 2015 and 2016, the FDA approved expanded label indications for lenalidomide and carfilzomib [3]. Clearly, the access to new and better drugs reflected in longer progression-free survival (PFS) and OS is fantastic for patients with a diagnosis of MM. However, from a drug development/regulatory perspective, the success imposes new challenges. As a result of the long duration of benefit currently achieved treating a patient with newly diagnosed MM, it will now take several years to establish a new therapy as superior to an existing alternative. This will have an enormous impact on future drug development.

2. Three types of support used in making clinical decisions

Physicians seeking support for clinical decisions typically use three types of information: (1) survival data from randomized phase III clinical trials, (2) surrogate endpoint data from single-arm or randomized phase II or phase III clinical trials, and (3) expert guidelines, based on reasonable belief (Table 1) [4].

3. Survival data

Although survival data are self-explanatory, an average survival of 10 or more years [2] means it will take a long time for studies with a survival endpoint to mature. Thus one can expect that in the future the use of survival data will decline and be replaced by surrogate endpoints. This logic is particularly true for drug development focusing on newly diagnosed MM and early relapse of MM. For multiply relapsed MM, the unmet clinical need remains high and surrogate endpoints have an already established role (Table 2).

4. Surrogate endpoints

Surrogate endpoints have been used for drug approval for several years. The FDA has acknowledged response rates and PFS as surrogates for OS and these have been sufficient for accelerated approval of several MM drugs (Table 2). With recent improvements in clinical outcomes, the field of MM has been forced to seek new surrogate endpoints for drug approval. As a necessary and logical next step, clinical studies have explored strategies to detect minimal residual disease (MRD) and attempted to establish its correlation with clinical outcomes. A recent meta-analysis found that MRD negativity (versus positivity) was associated with better PFS (hazard ratio [HR] = 0.35; $P < .001$) and OS (HR = 0.48; $P < .001$) [5]. Ongoing discussions at the FDA are supportive of MRD negativity becoming a regulatory endpoint for newly diagnosed MM in the coming few years [6].

5. Expert guidelines (based on reasonable belief)

Due to inherent delays in the delivery of results from extended clinical trials, expert guidelines based on opinions by leading cancer centers (eg, Memorial Sloan Kettering Cancer Center [MSKCC] and Mayo Clinic), national expert groups (eg, National Comprehensive Cancer Network **[**NCCN]), and other international and national groups have been developed. These guidelines represent “bridges of evidence” (based on reasonable belief) [4] until formal data become available. The NCCN guidelines are particularly important for American patients. In the United States, once a drug has obtained FDA approval, the drug also has approved reimbursement. Importantly, if an NCCN disease expert committee considers the evidence for a given therapy sufficient to warrant its use, it will be recommended in their compendia listing. The latter recommendation will be independent of the indication that led to FDA approval. Traditionally, Medicare will reimburse therapies in the NCCN compendia listing and, typically, insurance companies follow Medicare. Thus, a practical implication of the NCCN

Table 2
Selected drugs approved in the United States for the treatment of patients with relapsed or refractory multiple myeloma, using different approval types.

Drug	Approval type	Endpoint	Trial design	Year
Velcade (bortezomib)	Accelerated approval	Response rate	Single-arm trial: ORR 52%	2003
	Regular approval	TTP/OS	Randomized, open-label trial TTP: 6.2 mos (VD) *v*. 3.5 mos (D)	2005
Revlimid (lenalidomide)	Regular approval	TTP	2 randomized clinical trials: RD *v* D Study 1: 13.9 mos *v* 4.7 mos Study 2: 12.1 mos *v* 4.7 mos	2005
Kyprolis (carfilzomib)	Accelerated approval	Response rate	Single-arm trial: ORR-22.9%	2012
Pomalyst (pomalidomide)	Accelerated approval	Response rate	Phase II randomized, open-label trial POM-D *v* POM; ORR 33% *v* 8%	2013

TTP = time to progression; OS = overall survival; V = Velcade; D = dexamethasone; R = Revlimid; POM = pomalidomide; ORR = overall response rate.