3.69 Reporting of Postprotocol Therapies in Multiple Myeloma with Dr. Ghulam Rehman Mohyuddin

↗ Type	Plenary Session

We Discuss:

Plenary Session 3.69 Show Notes

Overview

Conversation with Dr. Ghulam Rehman Mohyuddin [1:05]

- **YouTube**
  - Watch this conversation on YouTube
- **Introduction**
  - "Manni" Mohyuddin, MD will be joining the faculty at the University of Utah in the Division of Hematology and Hematologic Malignancies

Reporting of Postprotocol Therapies and Attrition in Multiple Myeloma Randomized Clinical Trials [1:56]

- Published in JAMA Network Open
- **What is a protocol therapy? And what's the post-protocol therapy?**
    - A protocol therapy is the therapy that is pre-defined as part of the randomized trial
        - e.g., Intervention A versus Intervention B
    - A post-protocol therapy is treatment given after a patient progresses on a clinical trial
        - These therapies are incredibly important because endpoints such as progression-free survival (2+) or overall survival are impacted by post-protocol therapies
            - Quality of life is also impacted by post-protocol therapy
                - What we really care about is quality of life across the patient's journey from the point of randomization until death or cure occurs (instead of just a snap shot)
                    - Patient Experience Captured by Quality-of-Life Measurement in Oncology Clinical Trials
                        - Published by Haslam et al. in JAMA Network Open
    - The current paradigm of how trials are designed across oncology don't really help us in sequencing treatments
        - This is partly due to the incentive structure from a pharmaceutical company standpoint
            - There is more to gain, financially speaking, from designing trials that bring treatments to earlier lines of therapy vs. designing trials for sequencing
- **Methodology [9:47]**
    - Dr. Mohyuddin and his team looked at RCTs from 2005-2019
        - Trials that focused exclusively on supportive treatment, infection prevention, or various stem cell mobilization methods were omitted

> *"The primary outcomes were the proportion of RCTs that reported postprotocol therapies and, in trials that reported postprotocol therapies, the percentage of patients who received no further therapy.*
> ~
> *For quantitative estimation of attrition and receipt of subsequent therapy, we only included studies that clearly reported the number of patients receiving subsequent therapies in both the control and intervention arm. Studies that only reported on a particular type of therapy or only on one arm were excluded from the quantitative analysis." Mohyuddin et al.*

- 103 studies that met their inclusion criteria were analyzed to find the proportion that reported on post-protocol therapies

Results [11:50]

> *"We found 45 of the 103 RCTs (43.7%) that reported subsequent treatments in the original article or in any follow-up publication or abstract. Among these 45 trials, the subsequent treatments were reported in the main article in 11 studies (24.4%), in a supplemental appendix in 11 studies (24.4%), and in a subsequent abstract presentation in 23 studies (51.1%)." Mohyuddin et al.*

- **Examples from the literature mentioned:**
  - SWOG S0777
    - *This trial did not report subsequent treatments in a follow-up publication*
      - Due to the lack of a follow-up publication, it is unclear how many patients randomized to lenalidomide and dexamethasone received bortezomib once they progressed
  - GIMEMA-MMY-3006
    - *This paper serves as a counter example*

> *"With a median follow-up of 124.1 months and transparent reporting of balanced subsequent therapies in both arms, there was a clinically meaningful OS benefit for patients receiving triplet therapy induction vs a doublet therapy induction of thalidomide and dexamethasone, highlighting the value of triplet therapy as induction." Mohyuddin et al.*

        - When post-protocol therapies and additional data are presented, it helps clinicians and researchers form better conclusions and ask questions
            - Additional example
                - IFM 2009 Study

- **RCTs funded by pharmaceutical companies were more likely (55.3%) to report post-protocol therapies than RCTs funded by cooperative groups (33.9%)**
    - Dr. Prasad believes this may be due to:
        1. Pharmaceutical companies having more resources
        2. Pharmaceutical companies love to hit "checkboxes"
        3. Companies have every incentive to collect as much data as possible
- **Attrition**
    - Roughly ~50% of patients in frontline and relapsed/refractory trials went on to receive any further lines of therapy
        - This data is in line with research by Fonesca et al.

> "That's disappointing– you would have expected more patients to get subsequent therapies so those results were very sobering." - Dr. Mohyuddin

- **Pivotal trials [24:00]**
    - MAIA
    - ALCYONE

Table 2. Pivotal Frontline Trials and Their Reporting/Description of Postprotocol Treatments

Trial	Enrolled in US	Intervention/control	Subsequent treatment reported	OS advantage reported	Magnitude of OS advantage reported		Observations regarding subsequent treatment
					Median	HR (95% CI)	
SWOG 0777[4]	Yes	Bortezomib, lenalidomide, dexamethasone vs lenalidomide, dexamethasone	No	Yes	NR vs 69 mo	0.71 (0.54-0.93)	NA
MAIA[9]	Yes	Dexamethasone, lenalidomide, daratumumab vs lenalidomide, dexamethasone	Yes	No	NA	NA	None of the 3 most common regimens used at progression (bortezomib; bortezomib, cyclophosphamide, dexamethasone; bortezomib, melphalan, prednisone) for control arm were daratumumab-containing regimens
ALCYONE[10]	No	Daratumumab, bortezomib, melphalan, prednisone vs bortezomib	Yes	Yes	36-mo OS, 78% vs 67.9%	0.60 (0.46-0.80)	Only 10% of patients in control arm received a daratumumab-containing regimen at first progression
VISTA[11]	Yes	Bortezomib, melphalan, prednisone vs melphalan, prednisone	Yes	Yes	56.4 vs 43.1 mo	0.70 (Not reported) $P = .0004$	43% Of patients in melphalan, prednisone arm received subsequent bortezomib
MM-015[12]	No	Melphalan, prednisone, lenalidomide vs melphalan, prednisone vs melphalan, prednisone, lenalidomide continuously	Yes	No OS	NA	NA	61.7% Of patients in melphalan, prednisone, arm received subsequent lenalidomide
Rajkumar et al[13]	Yes	Lenalidomide, low-dose dexamethasone vs high-dose dexamethasone	Yes	Yes (at 1- and 2-y mark)	1-y OS: 96% (range, 94%-99%) vs 87% (range, 82%-92%)	NA	All patients crossed over to low-dose dexamethasone when clear signal of survival benefit was seen, and the survival curves merged at 3-y mark
FIRST[14]	Yes	Lenalidomide, dexamethasone vs melphalan, prednisone, thalidomide	Yes	Yes	59.1 vs 49.1 mo	0.78 (0.67-0.92)	Similar treatments at progression, bortezomib-based regimen most commonly used

Abbreviations: HR, hazard ratio; NA, not applicable; NR, not reached; OS, overall survival.

Mohyuddin et al.

- **Crossover [29:50]**
  - A short summary of crossover

> *"There is one special feature that sometimes occurs in cancer random- ized trials, which is vital to understand. That feature is called crossover, or unidirectional crossover. Crossover means that, at some point, patients who were assigned to the control arm of a trial (either the established standard of care drug or placebo) are allowed to receive the new drug after they have progressed" - Dr. Prasad*

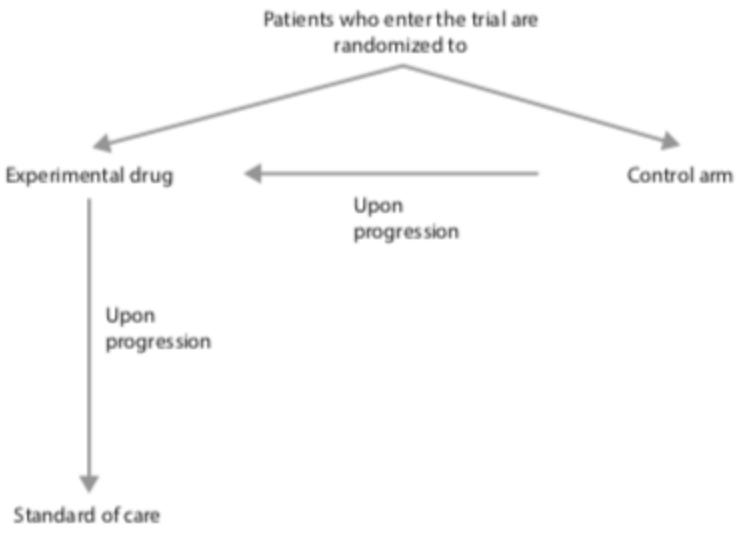

Figure 9.1. Crossover in randomized trials

Vinay Prasad in Malignant

- Relapsed/Refractory Trials

Table 3. Pivotal Relapsed/Refractory Trials and Their Reporting and Description of Postprotocol Treatments

Trial	Enrolled in US	Intervention/control	Subsequent treatment reported	OS advantage reported	Magnitude of OS advantage reported		Observations regarding subsequent treatment
					Median	HR (95% CI)	
CASTOR[15]	Yes	Daratumumab, bortezomib, dexamethasone vs bortezomib, dexamethasone	Yes	Not at this time	NA		Subsequent treatment not reported in updated publications other than 81 patients in bortezomib arm, dexamethasone arm received daratumumab monotherapy at progression[16,17]
POLLUX[18]	Yes	Daratumumab, lenalidomide, dexamethasone vs lenalidomide, dexamethasone	Yes	Not yet	NA		Most patients with MM progression (77.8%) in lenalidomide, dexamethasone arm received daratumumab monotherapy at progression
ASPIRE[2]	Yes	Carfilzomib, lenalidomide, dexamethasone vs lenalidomide, dexamethasone	Yes	Yes	48.3 vs 40.4 mo	0.79 (0.67-0.95)	Only 2% of patients in lenalidomide, dexamethasone arm received carfilzomib subsequently
ELOQUENT-2[3]	Yes	Elotuzumab, lenalidomide, dexamethasone vs lenalidomide, dexamethasone	Yes	Yes	48.3 vs 39.6 mo	0.82 (0.68-1.00)	Elotuzumab not given to control arm on progression
ENDEAVOR[19]	Yes	Carfilzomib, dexamethasone vs bortezomib, dexamethasone	Yes	Yes	47.6 vs 40 mo	0.79 (0.65-0.96)	Only 8% of patients in bortezomib arm received carfilzomib subsequently

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- **Other literature mentioned:**
  - BOSTON
    - Everyone's favorite trial
  - The Response Rate of Alternative Treatments for Drugs Approved On the Basis of Response Rate
    - Haslam et al. in the IJC

- Limitations in Clinical Trials Leading to Anticancer Drug Approvals by the US Food and Drug Administration
  - Hilal et al. in JAMA IM
- MONARCH 2
  - Sledge in JCO

Plenary Session is a podcast on medicine, oncology, & health policy.

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