Paper TA09

A Step-by-Step Programming Approach to Summarize Best Response in Patients with Multiple Myeloma Who Had Positive and Negative MRD Test Results

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ABSTRACT

Minimal Residual Disease (MRD) test has been considered the most relevant prognostic factor in Multiple Myeloma (MM). MRD testing is done to see whether cancer treatment is working and what could be further course of action for new or ongoing treatments. This test can find even the smallest amount of cancer cells that may be left in the body after treatment and highly efficient method to detect even one cancer cell among a million normal cells.

Summarizing the best response in patients with MRD test results for a given line of chemotherapies often appears challenging for statistical programmers. A stepwise logical approach on how to combine various data sources for a patient may be helpful to generate a detailed summary report of the best response with MRD Positive and MRD Negative test results. Patients with negative MRD test results display significantly longer survival as compared to those with positive MRD test results.

INTRODUCTION

MM is a type of blood cancer that develops in plasma cells inside the bone marrow. In healthy bone marrow, normal plasma cells make antibodies to protect the body from infection. Whereas in patients with MM, plasma cells are transformed into cancerous cells that grow out of control and reduce normal blood cells (RBCs, WBCs, and platelets) which help fight infection. These malignant plasma cells then produce an abnormal antibody called M protein, high levels of which are a characteristic feature of MM.

Measurable or minimal residual disease (MRD) testing is used mainly to identify patients at higher or lower risk of relapse. Also, to see if the cancer treatment is working and to determine further treatment plans. MRD testing is mainly used in blood cancers such as leukemia, lymphoma, and MM, but is being studied in other cancers as well. This test can be used to find how well cancer has responded to the treatment received.

There are three ways to assess MRD in MM i.e., Flow cytometry, NextGen sequencing (genetic markers) and imaging. MRD test results are categorized into positive and negative. Treatment of MM has substantially changed over the past decade with the introduction of several classes of new effective drugs. Identifying the best response, based on each of these two categories of MRD test results can inform treatment decisions for better clinical outcomes. Please note, for the purpose of this paper, the best response is based on investigator assessed response data.

IMWG Response Criteria in Multiple Myeloma

The International Myeloma Working Group (IMWG) provides guidance on response evaluation criteria as shown in Table 1 below.

Table 1

Definition of response according to the last classification of the IMF.

Categories of response according to IMF 2011	Level of detection
PR	MC < 50%
VGPR	MC < 90%
nCR	MC 0.1–0.5 g/dl (EF−/IF+)
CR	MC ≤ 0,5 g/dl (IF−)
	PC in BM < 5%
Stringent CR	sFLC ratio +BM ICH
Immunophenotypic CR	sCR+ nonaberrant PC in 1,000,000 cells
Molecular CR	CR+ nonclonal plasma cells with sensitivity > 10^{-5}

In 2014, IMWG updated the guidance and added three specific biomarkers that can be used to diagnose the disease in patients who did not have CRAB features: a clonal bone marrow plasma cells greater than or equal to 60%, serum free light chain (FLC) ratio greater than or equal to 100, or more than one focal lesion on MRI. In addition, definition was revised to allow CT and PET-CT to diagnose MM bone disease. [CRAB: C = Calcium elevation; R = Renal insufficiency; A = Anemia; B = Bone abnormalities; nCR = near complete response]

Best Response by MRD Test results

In this paper, we are going to look at investigator assessed responses which are collected on CRF and how identification of the best response is related to MRD test results.

Example #1: To understand, let's look at Table 2 below that provides guidance on the layout of report. Here, the best response is identified based on overall MRD tests done and then grouped by MRD positive and negative test results. A detailed programming logic to produce Table 2 will be presented in the next section.

Table 2

Summary of Best Response by MRD Test Results

Response	All MRD Tests	MRD +ve Test	MRD -ve Test
CR/sCR	xx	xx	xx
VGPR	xx	xx	xx
PR	xx	xx	xx
MR	xx	xx	xx
SD	xx	xx	xx
PD	xx	xx	xx
Missing	xx	xx	xx

Note: CR – Complete Response, sCR – Stringent Complete Response, VGPR – Very Good Partial Response, PR – Partial Response, MR – Minimal Response, SD – Stable Disease, and PD – Progressive Disease

Example #2: Table 3 – Here, the best response is identified for all lines of treatments against overall MRD tests done and then grouped by MRD positive and negative test results. A detailed programming logic to produce Table 3 will be presented in the next section.

Table 3
Summary of Best Response by MRD Test Results
All Lines

Response	All MRD Tests	MRD +ve Test	MRD -ve Test
CR/sCR	xx	xx	xx
1st Line Response	xx	xx	xx
2nd Line Response	xx	xx	xx
3rd Line Response	xx	xx	xx
VGPR	xx	xx	xx
1st Line Response	xx	xx	xx
2nd Line Response	xx	xx	xx
3rd Line Response	xx	xx	xx
PR	xx	xx	xx
1st Line Response	xx	xx	xx
2nd Line Response	xx	xx	xx
3rd Line Response	xx	xx	xx
MR	xx	xx	xx
1st Line Response	xx	xx	xx
2nd Line Response	xx	xx	xx
3rd Line Response	xx	xx	xx
SD	xx	xx	xx
1st Line Response	xx	xx	xx
2nd Line Response	xx	xx	xx
3rd Line Response	xx	xx	xx
PD	xx	xx	xx
1st Line Response	xx	xx	xx
2nd Line Response	xx	xx	xx
3rd Line Response	xx	xx	xx
Missing	xx	xx	xx

Note: CR – Complete Response, sCR – Stringent Complete Response, VGPR – Very Good Partial Response, PR – Partial Response, MR – Minimal Response, SD – Stable Disease, and PD – Progressive Disease

Hypothetical Data Structure

To understand, let's look at a hypothetical data structure (Table 4a). This dummy data will be used as an example throughout this paper. The analysis dataset contains variables required to understand programming logic. Annotation of variables provide additional information about the data.

USUBJID = Unique subject identifier
LINE = Multiple lines of treatment received by a patient
PHASE = Various phases of treatment
SEQNUM = Treatment sequence number (also known as regimen number)
TSTART = Treatment start date,
TEND = Treatment end date

Source Data # 1

Table 4a: Dummy Data – Multiple Lines of Treatment

USUBJID	LINE	PHASE	SEQNUM	DRUG	TSTART	TEND
1001	1	Induction	1	ABC	12-Jun-10	08-Dec-11
1001	1	SCT	2	A	20-Dec-11	20-Dec-11
1001	1	Maintenance	3	Z	23-Apr-12	13-Feb-17
1001	2	Induction	4	CDE	23-Feb-17	12-Sep-17
1001	2	Consolidation	5	X	20-Sep-17	11-Nov-17
1001	2	Maintenance	6	Y	21-Dec-17	06-Feb-18
1001	3	Induction	7	Z	16-Feb-18	26-Jun-18
1002	1	Induction	1	ABC	12-Jun-10	08-Dec-11
1002	1	Consolidation	2	C	20-Dec-11	20-Dec-11
1002	2	Maintenance	3	BCD	23-Apr-12	13-Feb-17
1003	1	Induction	1	DEF	23-Feb-17	12-Sep-17
1003	1	SCT	2	D	20-Sep-17	11-Nov-17
1003	1	Maintenance	3	X	21-Dec-17	05-Feb-18
1003	2	Consolidation	4	XY	06-Feb-18	26-Jun-18
1003	2	Maintenance	5	XYZ	16-Aug-18	30-Sep-18

Table 4aa: Dummy Data – Transformed Data

USUBJID	LINE	LSTART	LEND
1001	1	12-Jun-10	13-Feb-17
1001	2	23-Feb-17	06-Feb-18
1001	3	16-Feb-18	26-Jun-18
1002	1	12-Jun-10	20-Dec-11
1002	2	23-Apr-12	13-Feb-17
1003	1	23-Feb-17	05-Feb-18
1003	2	06-Feb-18	30-Sep-18

The following lines of SAS code are submitted to create Table 4aa containing the start and end date per treatment line per subject.

```
proc sql noprint;
  create table t4aa as select subjid, line, min(tstart) as lstart format date9.,
              max(tend) as lend format date9.
  from t4a
  group by subjid, line;
quit;
```

Source Data # 2

Table 4b: Dummy Data – MRD Test Results Data as per CRF

USUBJID	MRDDT	MRDRSPN	MRDRSP
1001	12-Nov-10	1	MRD +ve
1001	13-Jan-11	2	MRD -ve
1001	23-Feb-11	1	MRD +ve
1001	27-Apr-11	1	MRD +ve
1001	25-May-11	1	MRD +ve
1002	23-Feb-17	2	MRD -ve
1002	17-Mar-17	2	MRD -ve
1002	19-Apr-17	1	MRD +ve
1002	21-May-17	1	MRD +ve
‘1002	16-June-17	1	MRD +ve
1003	23-Feb-18	1	MRD +ve
1003	17-Mar-18	2	MRD -ve
1003	19-Apr-18	2	MRD -ve
1003	21-May-18	1	MRD +ve
1003	05-Sep-18	2	MRD -ve

Source Data # 3

Table 4c: Dummy Data – Response Evaluation Data as per CRF

USUBJID	ASSESSYN	ASSDT	MMRESPN	MMRESP
1001	Yes	23-Feb-11	1	Complete Response (CR)
1001	Yes	13-Mar-11	6	Progressive Disease (PD)
1001	Yes	14-Jun-11	3	Partial Response (PR)
1001	Yes	23-Apr-17	2	Very Good Partial Response (VGPR)
1001	Yes	23-Jul-17	5	Stable Disease (SD)
1001	Yes	23-Aug-17	3	Partial Response (PR)
1001	Yes	25-Jun-18	7	Missing
1002	Yes	23-Feb-10	3	Partial Response (PR)
1002	Yes	06-Mar-10	6	Progressive Disease (PD)
1002	Yes	16-Jun-10	2	Very Good Partial Response (VGPR)
1002	Yes	11-Jul-11	6	Progressive Disease (PD)
1003	Yes	06-Aug-17	5	Stable Disease (SD)
1003	Yes	06-Sep-17	4	Minimal Response (MR)
1003	Yes	14-Aug-18	6	Progressive Disease (PD)
1003	Yes	06-Sep-18	7	Missing
1003	Yes	27-Sep-18	3	Partial Response (PR)

STEPS INVOLVED IN MERGING DATA

The first step is to create analysis data from different data sources. There are 3 different data sources we observe in the above examples.

Table 4aa - each subject receives multiple lines of treatment.
Table 4b - each subject undergoes multiple MRD tests for a certain period.
Table 4c - each subject has multiple responses collected.

Given multiple observations per subject, we create the cartesian product by merging all data using PROC SQL.

```
proc sql;
    create table t4abc as select a.*, b.mrddt, b.mrdrspn, b.mrdrsp, c.assdt, c.mmrespn, c.mmresp
    from t4aa a left join t4b b
    on a.subjid=b.subjid and a.lstart<=c.mrddt<=c.lend
    left join t4c c
    on a.subjid=c.subjid and a.lstart<=b.assdt<=c.lend
    order by a.subjid, a.line;
quit;

** Check to make sure no duplicates after merging all data **;
proc sort data=t4abc out=s_t4abc nodupkey;
  by subjid line mrdrspn mrdrsp mrddt assdt ;
run;
```

CHALLENGES

We see that each source data has multiple observations per subject and combining all three data by using DATA STEP MERGE may pose a risk. Hence, PROC SQL is more appropriate in this situation. Furthermore, here we are counting the number of best response cases for overall MRD tests done. The data structure is similar to occurrence data (OCCDS); with multiple MRD tests per subject. Sometimes, it may appear challenging to identify best responses when MRD test date lies outside of start and end date for a given treatment line i.e. between 1st and 2nd line or due to overlapping dates of treatment lines when both lines may have different start dates but same end dates.

Table 2 Programming Steps

To generate Table 2, the below program is submitted. Here counts are created based on response categories and MRD tests. The first column refers to MM response categories which are tabulated by MRD test: Overall, MRD +ve, and MRD -ve.

```
** Step 1(a). Identify Best response per subject from multiple responses **;
proc sql;
  create table bestresp as
  select subjid, mrdrspn, mrdrsp, min(mmrespn) as bestresp
  from s_t4abc
  group by subjid, mrdrspn, mrdrsp, mmrespn, mmresp;
quit;


** Step 1(b). Get counts of Best response by MRD overall tests **;
proc sql;
  create table mrd_all as
  select mrdrspn, mrdrsp, count(subjid) as bresp_mrd_all
  from bestresp
  group by mrdrspn, mrdrsp, bestresp;
quit;
```

```
** Step 1(c). Get counts of Best response by MRD +ve tests **;
proc sql;
  create table mrd_pos as
  select mrdrspn, mrdrsp, count(subjid) as bresp_mrd_pos
  from bestresp
  where mrdrsp = 'MRD +ve'
  group by mrdrspn, mrdrsp, bestresp;
quit;


** Step 1(d). Get counts of Best response by MRD -ve tests **;
proc sql;
  create table mrd_neg as
  select mrdrspn, mrdrsp, count(subjid) as bresp_mrd_neg
  from bestresp
  where mrdrsp = 'MRD -ve'
  group by mrdrspn, mrdrsp, bestresp;
quit;


** Step 1(e). Merge all to get final data for Table 2 **;
data tab2;
  merge mrd_all mrd_pos mrd_neg;
  by mrdrspn mrdrsp bestresp;
run;
```

Table 3 Programming Steps

The programming logic used for Table 3 is similar to that used for Table 2, except that line of treatment is also considered when deriving the best response counts. As shown in "Step 2(a)" below, table "bestresp" is created per subject, per MRD response and per treatment line (circled). Code 1(b) through 1(e) from Table 2 are the same.

```
** Step 2(a). Identify Best response per subject per treatment line from multiple responses **;
proc sql;
  create table bestresp as
  select subjid, mrdrspn, mrdrsp, line,  min(mmrespn) as bestresp
  from s_t4abc
  group by subjid, mrdrspn, mrdrsp, line, mmrespn, mmresp;
quit;
```

CONCLUSION

MRD testing to detect cancer cells in MM has been widely used and accepted. Many scientific papers on MRD tests results have been published which indicate its high sensitivity to detect 1 cancer cell in 1 million normal cells. MRD can show how well the medicine works at treating the cancer without having to wait months to see if the cancer returns. The author has tried to establish the relationship between the best response identified in MM and MRD test results with the help of different hypothetical data sources, programming logic and output reports. The report indicates that the best response is related to MRD negative tests.

Although the paper explains various concepts and data structure that may be helpful to statistical programmers, at the same time it also provides an opportunity to explore derived response based on defined criteria in IMWG guideline and protocol.

ACKNOWLEDGMENTS

The author would like to extend his sincere thanks to Ephicacy Lifescience Analytics for the opportunity to write and present this paper. Any brand and product names are trademarks of their respective companies.

RECOMMENDED READING

https://www.oncolink.org/cancer-treatment/procedures-diagnostic-tests/blood-tests-tumor-diagnostic-tests/testing-for-measurable-minimal-residual-disease-mrd

https://www.cancer.org/cancer/types/multiple-myeloma/about/what-is-multiple-myeloma.html

https://www.oncolink.org/cancer-treatment/procedures-diagnostic-tests/blood-tests-tumor-diagnostic-tests/testing-for-measurable-minimal-residual-disease-mrd

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4689894/

https://ascopubs.org/doi/full/10.1200/EDBK_159009?role=tab

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