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PREDICTING SURVIVAL OUTCOMES IN MYELOMA USING SURROGATE MARKERS

TESI DI DOTTORATO

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INTRODUCTION

During the last ten years, the number of randomized controlled trials (RCTs) evaluating various treatment strategies in Multiple Myeloma (MM) has increased. Studies are being conducted worldwide, including an increasing number of multicenter, international trials.[1] As the number of treatment options has increased over time, there has been considerable debate as to the most relevant endpoints in this disease. The International Myeloma Workshop Consensus Panel considers progression free survival (PFS) and overall survival (OS) as essential endpoints for efficacy in phase III trials.[2] In regulatory clinical trials, endpoint as PFS is meaningful in a disease, such as MM, because a significant prolongation of this endpoint can be reasonably indicative of clinical benefit.[1,3-5] PFS is an indicator of drug activity [6]and it is an appropriate endpoint for the approval of new drug in MM to avoid delays in getting new drugs into practice. However, OS should be considered the gold standard before adopting a particular treatment strategy as standard of care. Given the considerable improvement in overall survival (OS) seen in MM during the past decade, and the limited number of patients that can be enrolled into phase III trials, use of OS as trial endpoint results in long trial duration. However, given the long duration of follow up required of such trials we need to identify reliable predictors of improved OS early on. These early surrogate markers are not for early adoption of potential trial results, but to guide us in the design subsequent trial strategies ahead of time.

We designed this study to evaluate if a there is a minimum improvement on PFS that will translate into an OS benefit in a reasonably high proportion of trials, or if there is a threshold of PFS improvement below which an OS benefit is unlikely to happen. Prolongation of OS in MM is

almost always associated with prolonged PFS, but not the other way around[7-9]. Identification of such thresholds will allow us to make reasonable hypothesis for future trials designs without having to wait for a long period for the mature results from existing clinical trials. The primary objective of our project was to investigate whether there was a required minimum PFS difference between two arms in phase III randomized controlled trials (RCTs) that can be used as a predictor of benefit in overall survival (OS). Secondary objectives were to explore if there was a minimum threshold for VGPR rate and CR rate difference between two arms that will predict PFS difference or OS difference in RCTs.

DESIGN AND METHOD

Data sources and search

We performed a PUBMED search to identify potentially relevant randomized controlled trials (RCTs) using the terms “Multiple myeloma”, “Randomized clinical trial”, “phase III/3 ”, published between January 1992 to January 2012. We also scanned references of abstracts presented at the American Society of Hematology (ASH) using the same terms between January 2005 to August 2012; this was supplemented by manual searches of others clinical trials. We included only the RCTs that reported CR, VGPR, progression-free survival or event-free survival (PFS/EFS), time to progression (TTP), overall survival (OS) on intention-to- treat basis. We also examined the relationships within different subgroups such frontline, relapse or refractory, stem-cell transplantation (SCT), maintenance trials, chemotherapy (CHT) and SCT, old and new drug trials.

Statistical analysis

We used both absolute differences in the survival improvement (in months) and response rates between the two arms, as well as proportional improvements for the purpose of analysis. Descriptive statistics were used to summarize the minimum threshold PFS, CR AND VGPR median differences respectively. All analyses were performed using JMP Software Version 9.0.1.

RESULTS

Literature search results

The initial literature search identified 314 papers for review; 17 other papers were identified by manual research. Assessment of these publications resulted in identification of 75 RCTs. All 75 RCTs were in PHASE III and presented an adequate randomization procedure.[3-5,7,10-82]. Of the 75 RCTs studied, 17 (22%) had statistically significant improvement in OS on intent to treat analysis (p-value ≤ 0.05)[3,5,18,30,34,36,37,39,40,46-48,50,65,68,74,79,81]. Data to estimate median improvement in PFS was present in all of these trials. One of these trials (Facon et al [48]) had three arms, in which the arm with significant OS advantage was significantly better than each of the two other arms, and was therefore considered for purposes of this analysis as two trials. Thus 18 trials were included to estimate the magnitude of PFS benefit that resulted in a significant OS advantage (Table 1).

Magnitude of PFS benefit required for survival improvement

We found that the minimum improvement in median PFS/TTP required to produce a significant improvement in OS was at least 2.5 months or more [34,39,46] [3,5,18,30,36,37,40,47,48,50,65,68,74,79,81]. We observed that this number varied depending on the stage of the disease and the type of treatment . Of the 18 trials, 11 were frontline (61%)[30,34,36,40,46,48,68,74,79,83], 4 were relapsed (22%)[3-5,84], 1 was consolidation (6%)[50,81] and 2 was maintenance (11%)[18,39]. In frontline trials , all 11 trials had a PFS benefit of at least 4 months or more (range, 4-12.4 months). In fact, in 73% of frontline trials, the minimum improvement in PFS required to observe a significant improvement in OS was 7 months or more. In all 4 relapse or refractory trials the PFS benefit associated with significant OS improvement was 2.5 months or more. In the 1 consolidation trial that had a significant OS benefit, the PFS improvement was 6 months. In the 2 maintenance trials, the PFS improvement was 12.2 months or more.

We then assessed the magnitude of PFS benefit required for OS improvement based on treatment modality. In the 14 chemotherapy trials the PFS benefit needed for OS improvement was at least 2.5 months[3,5,18,30,34,36,37,39,40,46-48,68,79] while in the 4 SCT trials, the minimum PFS benefit was 6 months or more[48,50,65,74,81]. In 13 trials that used new agents (thalidomide, lenalidomide, or bortezomib), the minimum improvement in median PFS required for an OS benefit was 2.5 months [3,5,18,30,36,37,39,40,46-48]; the corresponding value for the 5 trials using older agents was 5 months[50,65,81] [68,74,79]

Magnitude of complete response benefit required for survival improvement

The improvement in CR required for survival improvement could be calculated in 16[3-5,18,34,36,39,40,46,48,50,68,74,79,81,84] of the 18 trials in which CR rates were reported . In newly diagnosed myeloma (9 trials)[34,36,40,46,48,68,74,79], CR improvements appeared to be widely variable, ranging from -5% (arm with survival improvement having worse CR rate by -5%) to 36%, with no particular pattern relative to type of therapy administered and the minimum threshold needed for survival benefit. In 2 trials, CR was either not improved or was worse in the arm with superior survival. In 4 trials (50%) the improvement in CR was less than 10%, while in 2 trials an absolute increase in CR rates of over 25% was seen.

We tried to determine the minimum increase in VGPR that is associated with improved OS, but VGPR rates were reported only in 5[34,39,40,46,74] of the 18 trials , and therefore could not be accurately computed.

PFS benefit in clinical studies with no significant improvement in OS

Of 75 RCTs, 58 (77%) hadn't statistically significant improvement in OS[7,11-17,19-29,31-33,35,38,41-45,48,49,51-54,56-64,66,67,69-73,75-78,82,85-87]. 5 of 58 clinical trials with more than two arms[14,17,44,52,86] were considered as different trials with comparison of each pair of arms being a different two-arm trial.

The PFS improvement could be calculated in 48 of 65 RCTs with no significant benefit in OS. Of 48 trials, 27 (56%)[7,12,14,16,17,21,24,31,33,35,41,42,45,52,54,59,60,62,64,67,76,85,88] were newly diagnosed, 13 (27%)[15,19,23,38,44,49,56,69,77,86] were in relapse, 2 (4%)[43,82] were in consolidation and 7 (14%)[13,28,32,63,70,71,75] were in maintenance . In these trials the minimum PFS improvement was

0.37, 0.1, 26 and 5.1 months respectively. Sixteen of 49 RCTs (33%) with no OS improvement had a PFS improvement less than the minimum threshold of 2.5 months that we had identified as being required for OS benefit.

Of the 27 newly diagnosed myeloma trials, 10 (37%) had PFS improvement less than the minimum threshold of 4 months that we had identified as being required for OS benefit. Among all newly diagnosed myeloma trials (11 with survival improvement and 27 without), a PFS improvement of less than 4 months was never associated with survival benefit, while an improvement of 4 months or more was associated with a 39% probability of a significant OS benefit (11 of 28 trials).

Similarly of 13 relapsed MM trials, 9 (69%) had PFS improvement less than the minimum threshold of 2.5 months that we had identified as being required for OS benefit. Among all relapsed myeloma trials (4 with survival improvement and 13 without), a PFS improvement of less than 2.5 months was never associated with survival benefit, while an improvement of 2.5 months or more was associated with a 50% probability of a significant OS benefit (4 of 8 trials).

All 2 consolidation trials had PFS improvement more than the minimum threshold of 6 months. Among all consolidation myeloma trials (1 with survival improvement and 2 without), a PFS improvement of less than 6 months was never associated with survival benefit, while an improvement of 6 months or more was associated with a 33% probability of a significant OS benefit (1 of 3 trials).

On 7 maintenance trials, 2 (29%) had PFS improvement less than the minimum threshold of 12.2 months. Among all maintenance trials (2 with survival improvement and 2 without), a PFS improvement of less than 12.2 months was never associated with survival

benefit, while an improvement of 12.2 months or more was associated with a 50% probability of a significant OS benefit (2 of 4 trials).

Of the 43 chemotherapy and of 6 transplant myeloma trials, 15 (35%) and 2 (33%) had PFS improvement less than the minimum threshold of 2.5 and 6 months that we had identified as being required for OS benefit. Among all chemotherapy and transplant myeloma trials (12 and 4 with survival improvement and 43 and 6 without), a PFS improvement of less than 2.5 and 6 months was never associated with survival benefit, while an improvement of 2.5 and 6 months or more was associated with a 30% and 50% probability of a significant OS benefit (12 and 4 of 40 and 8 trials), respectively.

Of the 30 new and of 19 old myeloma trials, 12 (40%) and 7 (37%) had PFS improvement less than the minimum threshold of 2.5 and 5 months that we had identified as being required for OS benefit. Among all new and old drug myeloma trials, respectively, (11 and 5 with survival improvement and 18 and 11 without), a PFS improvement of less than 2.5 and 5 months was never associated with survival benefit, while an improvement of 2.5 and 5 months or more was associated with a 38% and 31% probability of a significant OS benefit (11 and 5 of 29 and 16 trials), respectively.

CR benefit in clinical studies with no significant improvement in OS

Of 75 RCTs, 48 (64%) did not show a statistically significant improvement in OS.

Of 48 trials, 31 (65%) were newly diagnosed, 9 (19%) were relapsed patients, 4 (8%) on consolidation therapy and remaining 4 (8%) analyzed maintenance therapy (Table). In these

trials the minimum CR improvement was 19, 5, 3 and 3 months respectively. Sixteen of 49 RCTs (33%) with no OS improvement had a PFS improvement less than the minimum threshold of 2.5 months that we had identified as a requirement for achieving a statistically significant OS benefit.

Of the 31 newly diagnosed myeloma trials, 12 (39%) had CR improvement less than the minimum threshold of 3.2 months that we had identified as being required for OS benefit. Among all newly diagnosed myeloma trials (7 with survival improvement and 31 without), a CR improvement less than 3.2 months was never associated with a survival benefit, while an improvement of 3.2 months or more was associated with a 27% probability of a significant OS benefit (7 of 26 trials).

Similarly of 9 relapsed MM trials, 5 (56%) had PFS improvement less than the minimum threshold of 2 months that we identified to be a requirement for attaining an OS benefit. Among all relapsed myeloma trials (4 with survival improvement and 5 without), a CR improvement of less than 2 months did not correlate with a survival benefit, while an improvement of 2 months or more was associated with a 44% probability of a significant OS benefit (4 of 9 trials).

All 4 consolidation trials had CR improvement more than the minimum threshold of 10 months. Among these trials (2 with survival improvement and 3 without), a CR improvement of less than 10 months did not associate with a corresponding survival benefit, while an improvement of 10 months or more was associated with a 40% probability of a significant OS benefit (2 of 5 trials).

On 4 maintenance trials, 1 (25%) had CR improvement less than the minimum threshold of 2 months. These trials (2 with survival improvement and 3 without) showing a CR improvement of less than 2 months was unassociated with survival benefit, while an improvement of 2 months or more showed an association with a 40% probability of a significant OS benefit (2 of 5 trials).

Of the 42 chemotherapy and of 6 transplant myeloma trials, 12 (29%) and 2 (33%) had CR improvement less than the minimum threshold of 2 and 5 months that we identified as a requirement to obtain an OS benefit. Amongst all chemotherapy and transplant myeloma trials (11 and 4 with survival improvement; 30 and 4 without), a CR improvement of less than 2 and 5 months was not associated with survival benefit, while an improvement of 2 and 5 months or more was associated with a 27% and 50% probability of a significant OS benefit (11 of 41 and 4 of 8 trials), respectively.

Of the 28 new and 20 old myeloma trials, 7(25%) and 14 (70%) had CR improvement less than the minimum threshold of 2 and 10 months respectively that we had identified to correlate with a significant OS benefit. Among all new and old drug myeloma trials (11 and 4 with survival improvement; 21 and 6 without), a CR improvement not reaching 2 and 10 months respectively was not associated with a survival benefit, while vice versa showed a correlation with a 34% and 40% probability of a significant OS benefit (11 of 32 and 4 of 10 trials), respectively.

DISCUSSION

Although RCTs are powerful instruments that help in defining the optimal method of interpreting the meaningful impact the treatment has on patients, they require prolonged follow up, need a large set of eligible patients and sometimes present with difficulties during randomization or recruitment along with significant costs.

Endpoints such as PFS and OS are the principal indicators to assess efficacy of therapies employed in clinical studies.

While Overall survival is the mainstay of measuring the full impact of the response to treatment, it requires a long follow-up period (over 5 years) before any inference could be drawn from initial response. PFS/TTP may or may not translate into overall survival benefit[89]; it may need a large sample size before significant results are achieved.

PFS is the recommended method to present trial results and it is considered an excellent surrogate marker for overall survival duration[89,90]. Hence in recent years the use of PFS has increased in all phase III RCTs.

In Oncology there has been an ongoing debate over the importance of a statistically significant improvement in PFS in the absence of a proven favorable impact on overall survival. We performed this study to investigate a minimum value of PFS improvement (the difference between ARM A and ARM B) which could possibly translate into OS benefit and hence provide a methodical guideline which could be used during the future development of Multiple Myeloma phase III RCTs.

We analyzed of 18 randomized phase III trials that reported an OS benefit. This helped us to identify a minimum PFS of 2.5 months as the minimum threshold value needed to achieve

a statistically significant benefit in OS. This was confirmed by further analyzing sixteen of 49 (33%) RCTs where no OS benefit was attained where the PFS was reported less than 2.5 months.

This minimum value of PFS varies with disease phase and the type of therapy used. In both, the frontline and relapsed RCT's that showed an OS improvement , the minimum threshold value of PFS benefit was 4 months and 2.5 months respectively while in 37% and 69% newly diagnosed and relapsed trials without an improved OS the reported PFS benefit was less than 4 and 2.5 months, respectively. This improvement of 4 and 2.5 months or more was associated with a 39% and 50% probability of a significant OS benefit in all newly diagnosed and relapsed trials (significant and non-significant with a PFS improvement over 4 months). Those trial with no significant OS benefit but showing a minimum PFS improvement of 4 and 2.5 months, respectively, could report an improvement in OS benefit by increase their study power with an longer follow up or an increase in the number of patients enrolled.

Amongst OS significant trials we found 1 consolidation trial where the minimum PFS improvement was 6 months; 2 other consolidation trials with no OS significant reported a minimum PFS benefit more than 6 months with a 33%probability of a significant OS benefit in all consolidation trials (significant and non-significant with a PFS improvement over 6 months).

In 2 maintenance trials, the minimum PFS benefit needed to achieve a significant OS improvement was 12.2 months. In 29% of non- significant OS, maintenance trials a minimum PFS improvement under 12.2 months was never associated with survival benefit , but we observed an high probability (50%) of a significant OS benefit among all maintenance trials, with or without significant OS but with minimum PFS improvement more than 12.2 months.

In chemotherapy and in transplant RCTs that showed an OS improvement , the minimum value of PFS benefit was 2.5 and 6 months respectively while 15% and 2% of chemotherapy and transplant trials without survival improvement reported a PFS benefit under 2.5 and 6 months, respectively. An improvement of 2.5 and 6 months or more was associated with 30% and 50% probability of a significant OS benefit respectively in all chemotherapy and transplant trials.

Finally, our analysis about new and old drug trials showed a minimum PFS benefit of 2.5 and 5 months respectively. 40% novel and 37% old drug trials without a survival benefit reportedly achieved a PFS less than 2.5 and 5 months respectively. An improvement of 2.5 and 5 months or more was associated with 38% and 31% probability of a significant OS benefit in all the new and old drug trials respectively.

It will be useful for future trials to regularly interpret the PFS benefit seen.

We also calculated the minimum CR improvement to achieve a statistically significant benefit in OS, but the data presented wide variability ranging from -5% to 36% making it unsuitable for our purpose. There were also no particular pattern relating the type of therapy administered and the minimum threshold needed for survival benefit.

Lack of adequate data on the VGPR achieved in various trials hindered the analysis of VGPR for our project.

In conclusion, the challenges encountered during prolonged follow up before OS benefits can be interpreted, along with the treatment associated burgeoning costs could be efficiently managed by keeping the threshold PFS value in consideration, which could be a pivotal surrogate marker for predicting the trends in OS. But the current data is still immature

for such an interpretation and underpowered trials make the analysis of OS further challenging.

We are limited by lack of data on Multiple Myeloma clinical trials showing OS significance.

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Study	Year of publication	ARM A	ARM B	Phase of MM	PFS/TTP median ARM A	PFS/TTP median ARM B	PFS/TTP(ARM A-ARM B)	p value(PFS)	OS (months) ARM A	OS (months)ARM B	p value (OS)
Facon et al.	2007	MPT	MP	New	27,5	17,8	9,7	<0.001	51,6	33,2	0,0006
J. F. San-Miguel et al.	2008	VMP	MP	New	24	16,6	7,4	<0.001	NR	NR	0.008
C. Hulin et al.	2009	MPT	MP	New	24,1	18,5	5,6	0,001	44	29,1	0.028
Zervas et al.	2007	TVAD-doxil	VAD-doxil	New	NR (at least 30 months)*	23	at least 7 months*	0,0013	NR	NR	0.037
P. Wijermans et al.	2010	MPT	MP	New	13	9	4	<0.05	40	31	0.05
Facon et al.	2007	MPT	MEL100	New	27,5	19,4	8,1	0,0002	51,6	38.3	0.027
Ludwig et al.	2009	MP	TD	New	20,7	16,7	4	0,1	49,4	41,5	0,024
N. Keldsen et al.	1993	MP	NOP	New	21	16	5	0,8	31	14	0.02
J. A. Child et al.	2003	Intensive therapy	Standard therapy	New	31,6	19,6	12	<0.001	54,1	42,3	0.04
M. Attal et al.	1996	High dose ASCT	Conventional Dose CCT	New	27	18	9	0,01	60	37,4	0.03
A. Palumbo et al.	2004	MEL100	MP	New	28	15,6	12,4	<0.0001	58+	42.5	0,0005
Bruno et al./L. Giaccone et al.	2007	Auto MEL200/200	Auto MEL 200/Allo TBI	Consolidation	33	39	-6	0,07	63,6	NR	0,03
Spencer et al.	2009	Thal	Control group	Maintenance	30,5	18,3	12,2	<0.01	NR	NR	0.004
McCarthy, P. L. et al.	2012	Len	Placebo	Maintenance	39	21	18	<0.001	NR	NR	0.03
D. M. Weber et al.	2007	Len/Dex	Placebo/Dex	Relapse/Refractory	11,1	4,7	6,4	<0.001	29.6	20.2	<0.001
P. G. Richardson et al.	2007	Bortezomib update	High-Dex initial	Relapse/Refractory	6,2	3,5	2,7	NA	29.8	23.7	0.027
R. Z. Orlowski et al.	2007	PLD+Bortezomib	Bortezomib	Relapse/Refractory	9	6,5	2,5	0,00026	NR	NR	0.03
M. A. Dimopoulos et al.	2007	Len/Dex	Placebo/Dex	Relapse/Refractory	11,3	4,7	6,6	<0.001	NR	20.6	<0.001