Achieving Complete Response in Multiple Myeloma: Do We Need to Change the Definition?

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Abstract

Multiple myeloma is a B cell neoplasm with monoclonal plasma cell expansion. The incidence varies between different countries from one per 100,000 to four per 100,000, probably due to under-diagnosis in developing countries. The therapeutic goal for multiple myeloma is prolonged progression free survival and overall survival. In recent years, it has been possible to detect smaller amounts of residual tumors through diagnostic and monitoring tools, such as IgH rearrangement qRT-PCR, multiparameter flow cytometry, microarray studies for methylation and imaging studies (e.g., positron emission tomography). A few studies have also proved the correlation between achieving molecular remission after treatment and progression free and overall survival. Therefore, the European Group for Blood and Marrow Transplant (EBMT) and International Myeloma Working Group (IMWG) uniform criteria seem to be inadequate to evaluate treatment response. Further studies on more sensitive tools are necessary for more accurate disease status evaluation. (J Intern Med Taiwan 2011; 22: 266-277)

Key words: Multiple myeloma, Minimal residual disease, Multiparameter flowcytometry, Real time RT-PCR

Introduction

Multiple myeloma is a B cell neoplasm characterized by clonal expansion of plasma cells in the bone marrow, which produce osteolytic bone disease and monoclonal protein. The incidence varies globally from one per 100,000 people to four per 100,000 people[1,2]. The cause of this variation may be due to underdiagnosis in developing countries. In Taiwan, the average age-adjusted incidence per 100,000 population was 0.75 from 1979 to 2003 according to the Taiwan National Cancer Registry[3]. In 2007, the average age-adjusted incidence had risen to 1.60 per 100,000 in male and 1.19 per 100,000 in female populations. The median age at diagnosis is about 62 years for males and 61 years for females. IgG type is the most common, followed by IgA type and

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light chain disease[2]. Active multiple myeloma from monoclonal gammopathy of undetermined significance (MGUS) generally develops after 3 to 5 years. The treatments are variable depending on the patients' age and performance status with a basic structure of primary induction therapy and maintenance therapy with/without hematopoietic stem cell transplantation (autologous single or tandem[4], or allogeneic[5]). The goal of treatment is to improve the patients' long-term outcomes, including prolonging progression-free survival (PFS) and overall survival (OS).

Two common staging systems, the Durie-Salmon staging system[5] and International Staging system[7,8], show that disease status may be related to overall survival (OS). Other disease related factors which are of prognostic importance for OS, are b2-microglobulin[7,9,10], albumin[7,10], C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels[11,12], cytogenetic abnormalities[10,11,13,14], plasma cell labeling index (PCLI)[9,12-15] and renal impairment[7,15-17].

An important factor associated with improved PFS and OS in MM is a patient's quality of response to treatment, and in particular the achievement of complete remission (CR). Several clinical trials have shown that the better the CR rate, the better the long-term outcomes, with longer PFS and OS (Table 1: with stem cell transplantation; Table 2: without transplantation; Table 3: relapse or refractory diseases). However, whether the current treatment response criteria, EBMT and IMWG, are good enough to predict better long-term outcomes require further investigation.

Current Definitions of Response

Many definitions of CR have been employed in clinical trials. Based on different sensitive methods to detect residual tumors, response criteria have evolved to include more stringent definitions of CR and other responses. The two most popular response criteria are the European Group for Blood and Marrow Transplant (EBMT) response criteria[18] and the more recent International Myeloma Working Group (IMWG) uniform response criteria[19] (Table 4). Except for CR, the IMWG criteria include the new category of stringent CR (sCR), reflecting the introduction of the free light chain assay and the use of sensitive immunohistochemistry or immunofluorescence techniques for defining a greater depth of remission than standard CR[19]. These criteria also feature the new category of very good partial response (VGPR), which incorporates near CR from modified EBMT criteria.

Diagnostic and Analytical Techniques for the Detection of Myeloma Disease Burden

There are many tools and methods to detect myeloma disease burden for the diagnosis and evaluation of disease status. Serum and urine protein electrophoresis, immunofixation, bone marrow aspiration/biopsy, and M protein analysis have been used for detection and follow-up. In recent years, the serum free light chain assay has been noted to be a more sensitive tool to detect tumor burden which is related to survival rate. This assay is included in the IMWG uniform response criteria[19].

Immunophenotyping with multiparametric flow cytometry (MFC) with several cell surface markers has been used to detect residual multiple myeloma cells. Paiva et al. used a combination of CD38/CD56/CD19/CD45 that can differentiate residual myeloma cells from normal plasma cells in more than 90% of cases, and added 1 or 2 additional monoclonal antibodies based on antigens such as CD28, CD117, CD33, and CD20 that were expressed at diagnosis. They reported a positive result of longer PFS in MFC negative patients 100 days after treatment in the GEM2000 protocol[20]. MFC uses a four-color direct immunofluorescence

technique to detect the phenotypic aberrancies at diagnosis (on the basis of three combinations: CD38/CD56/CD19/CD45, CD38/CD27/CD45/CD28 and microglobulin/CD81/CD38/CD117), as patient-specific probes.

One study showed a longer PFS in an MFC negative group in a subgroup of patients achieving CR and sCR[21]. Another sensitive method is real-time quantitative polymerase chain reaction (RT-PCR) which can detect residual tumor cells by selective immunoglobulin heavy-chain genomic rearrangements (IgH-R)[22]. Patient-specific IgH-Rs were amplified and direct sequenced from IgH-specific cDNA at diagnosis using consensus sense primers derived from the leader and first framework region (FR1), and a consensus antisense primer derived from FR4. Consensus probes were derived from FR3, as previously reported[76,77]. Other tools including immunohistochemistry/immunofluorescence have also been reported to detect myeloma cells[19].

Imaging studies, such as whole body bone X-ray, magnetic resonance imaging, and more recently, positron emission tomography (PET) scans are the other diagnostic, staging and evaluation of disease status techniques for multiple myeloma[23]. The sensitivity rates of those methods are shown in Table 5.

Chim et al., reported that 40% of 50 MM patients had methylation of at least one of seven genes which are related to Wnt pathway hypermethylation[24]. They also noticed that methylation of death-associated protein kinase (DAPK) was related to poor OS in a small number of MM patients (total 25 patients) treated by a staged approach, in which chemosensitive patients underwent autologous hematopoietic stem cell transplantation (auto-HSCT) while less chemosensitive patients received salvage therapy with bortezomib/thalidomide/dexamethasone (VTD) prior to auto-HSCT[25]. Brian et al. also showed different methylation patterns, detected by microarray, in nonmalignant cells and malignant cells, especial in t(4;14) myeloma cells[26]. These studies showed that hypermethylation in certain genes was a candidate to detect myeloma cells, in initial diagnosis or disease status follow up.

Improved Outcomes with Greater Depth of Response

CR is associated with improved survival in multiple myeloma patients. Many phase III and large phase II clinical trials have shown a positive relationship between CR and OS, EFS, and time to progression (TTP) in different induction chemotherapy treatments with auto-HSCT, without auto-HSCT and for relapse or refractory MM patients (Table 1, 2 and 3).

However, not all studies have shown that CR/maximal response is prognostic for OS or that there is an association between higher CR rates and improved outcomes[27-31]. Galli et al. reported no significant event-free and overall survival after second tandem auto-transplantation, except for the patients with a major reduction of myeloma burden at the end of induction therapy[28]. Lenhoff showed an association with relapse time, but not CR, and outcomes in patients younger than 60 years old[29]. This may be due to the definition of CR, which may not reach as low as residual tumor burden because of the sensitivity of the technique (Table 5). With the development of detection methods and a greater understanding of the pathophysiology of MM, few studies have analyzed the OS, PFS, and TTP under more sensitive detection tools defining CR. Minimal residual disease (MRD) may be evaluated, and thus CR more stringently defined, using MFC[20,21] and real time RT-PCR[22]. In a recent analysis with patients from the GEM2000 protocol (VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone/VBAD, vincristine, carmustine, doxorubicin, dexamethasone, induction

plus autologous stem cell transplantation), patients achieving MRD, detected by MFC, at day 100 after auto-HSCT, had better PFS (median 71 vs. 37 months, p<0.001) and longer OS (median not reached vs. 89 months, p=0.002)[20]. Moreover, MRD-immunofixation-negative (IFx-) patients and MRD-IFx+ patients had a significantly longer PFS than MRD+IFx- patients. In another study

Table 1. Response rates to Novel-Agent-Containing induction therapy, and clinical outcomes after auto-HSCT in Phase III and Large Phase II clinical trials

study	P't No	ORR (%)	Response rate (%)	Long term outcomes
IFM 2005-01[45]				
Vel/Dex	240	84	17CR;37CR/nCR; 57VGPR	1year PFS 69%; 1year OS 90%
VAD	242	79	9CR; 19CR/nCR; 38VGPR	1year PFS 60% 1year OS 88%
GIMEMA MMY-3006[46]				
VTD	226	NR	43CR; 55CR/nCR;	1year PFS 90%
TD	234	NR	76VGPR	1year OS 96%
			23CR; 32CR/nCR;	1 year PFS 80%
			58VGPR	1 year OS 91%
HOVON-50[47]				
TAD	268	88	31CR;66VGPR	EFS 34months; PFS 34months
				EFS 22months; PFS 25months
VAD	267	79	23CR; 54VGPR	
ECOG E1A00[48]		Before ASCT	Before ASCT	
TD	103	63	4CR	1year OS around 80%
Dexamethasone	104	41	0CR	1 year OS around 80%
GMSG[49]		Before ASCT	Before ASCT	
T-VAD-Doxil	117	81	15CR; 54VGPR	2 year PFS 59%, OS 77%
VAD-Doxil	115	63	12CR; 31VGPR	2 year PFS 45%, OS 65%
ECOG E4A03[50]		Before ASCT	Before ASCT	
RevHD	223	81	17CR;51VGPR	3 year OS 75%
RevLD	222	70	14CR;40VGPR	3 year OS 75%
Total therapy 2[51]				
Including T	323	NR	62CR	EFS 6 years; 8 year OS 57%
Without T	345	NR	43CR	EFS 4.1 years;8year OS44%
Total therapy 3[52-54]				
VTD-PACE induction	303	NR	60CR; 80CR/nCR	2 year EFS 85% 2 year OS 85%
Palumbo et al[55]				
PAD-MEL 100-Rev/Pred-Rev	102	99	43CR; 87VGPR	2 year PFS 78%; 2 year OS 84%

Abbreviations: CR: complete remission; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; GEM: Grupo Espanol de Mieloma; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; GMSG: Greek Myeloma Study Group; HOVON: Hemato-Oncologie voor Volwassenen Nederland; IFM: Intergroupe Francophone du Myeloma; MEL 100: melphalan 100mg/m^2; nCR: near CR; NR: not reported; ORR: overall response rate; OS: overall survival; PAD: bortezomib, doxorubicin and dexamethasone; PFS: progression free survival; Rev: lenalidomide; RevHD: lenalidomide, high-dose dexamethasone; RevLD: lenalidomide, low-dose dexamethasone; Rev/Pred: lenalidomide and prednisone; TAD: thalidomide, doxorubicin, and dexamethasone; TD: thalidomide and dexamethasone; T-VAD-Doxil: thalidomide, vincristine, liposomal doxorubicinand dexamethasone; VAD: vincristine, doxorubicin, and dexamethasone; Vel: bortezomib; Vel/Dex: bortezomib and dexamethasone; VGPR: very good partial response; VTD: bortezomib, thalidomide, and dexamethasone.

Table 2. Response rates to Novel-Agent-Containing first line therapy without undergoing auto-HSCT in Phase III and Phase II clinical trials

study	P't No	ORR (%)	Response rate (%)	Long term outcomes
VISTA[56]				
VMP	344	71	30 CR	DOR 19.9m, DOR(CR) 24m, TTP24m, TNT 28.1m, TFI 16.6m, 3year OS 72%
MP	338	35	4 CR	DOR 13.1m, DOR(CR) 12.8m, TTP 16.6m, TNT 28.1m, TFI 19.2m, 3year OS 59%
PETHEMA/GEM[57]				
GEM05MAS65				
VMP	130	78	22CR,36CR/nCR	2year TTP 81%, 2year OS 92%
VTP	130	81	27CR,37CR/nCR	2year TTP 83%, 2year OS 94%
GIMEMA[58]				
VMPT	221	84	35CR;51VGPR	3year PFS 71%, 3year TNT 80%, 3year OS 90%
VMP	229	78	21CR;42VGPR	3year PFS 56%, 3year TNT 78%, 3year OS 89%
IFM99-06[59]				
MPT	125	76	13CR;47VGPR	PFS 27.5m, OS 51.6m
MP	196	35	2CR; 7VGPR	PFS 17.8m, OS 33.2m
VAD + MEL100	126	65	18CR;43VGPR	PFS 19.4m, OS 38.3m
GISMM2001-A[60]				
MPT	167	69	16CR;29VGPR	TTP 24.7m, PFS 21.8m, OS 45m
MP	164	48	4CR;11VGPR	TTP 15.0m, PFS 14.5m, OS 47.6m
IFM01/01[61]				
MPT	113	62	7CR;21VGPR	PFS 24.1m, OS 44.0m
MP	116	31	1CR;7VGPR	PFS 18.5m, OS 29.1m
HOVON 49[62]				
MPT	165	62	29 ≧ VGPR	2year EFS 36%; 2year PFS 33%; 2year/4year OS 67%/36%
MP	168	47	9 ≧ VGPR	2year EFS 12%; 2year PFS 19%; 2year/4year OS 60%/25%
NMSG[63]				
MPT	182	57	13CR; 23VGPR	TTP ≒ 22m, PFS 14-15m, OS ≒ 35m
MP	175	40	4CR; 7VGPR	TTP ≒ 18m, PFS 14-15m, OS ≒ 35m
Ludwig et al[64]				
TD	145	68	2CR; 26 VGPR	TTP 21.2m; PFS 16.7m; OS 41.5m
MP	143	50	2CR; 13VGPR	TTP 29.1m; PFS 20.7m; OS 49.4m
ECOG MM003[65]				
TD	235	63	8CR, 44VGPR	TTP 22.6m; PFS 14.9m
Dexamethasone	235	46	3CR, 16VGPR	TTP 6.5m; PFS 6.5m
SWOG S0232[66]				
RevHD	100	84	22 CR	1year PFS77%; OS 93%
HD	98	53	4CR	1year PFS55%; OS 91%
GIMEMA[67]				
MPR				
Offidani et al[68]	50	98	34CR,58VGPR	3year TTP 78% 3year EFS 78% 3year OS 84%
ThaDD			<VGPR	3year TTP 40% 3year EFS 37% 3year OS 61%

Abbreviations: CR: complete response; DOR: duration of response; EFS: event-free survival; MEL100: melphaan 100mg/m^2; MP: melphalan, prednisone; MPR: melphalan, prednisone, lenalidomide; MPT: melphalan, prednisone, thalidomide; MTD: maximum tolerated dose; nCR: near CR; NMSG: Nordic Myeloma Study Group; ORR: overall response rate; OS: overall survival; PFS: pregression free survival; PR: partial response; RevHD: lenalidomide, highdose dexamethasone; SWOG: souhwest Oncology Group; TD: thalidomide, dexamethasone; TFI: treatment free interval; ThaDD: thalidomide, liposomal doxorubicin, dexamethasone; TNT: time to next therapy; TTP: time to progression; VAD: vincristine, doxorubicin, dexamethasone; VGPR: very good partial response; VMP: bortezomib, melphalan, prednisone; VMPT: VMP and thalidomide; VTP: bortezomib, thalidomide, prednisone.

Table 3. Response rates and long-term outcomes with Novel Agent-Containing Therapy in patients with relapsed/refractory MM: Phase III and Phase II trials

Study	P't NO	ORR (%)	Response rate (%)	Long term outcomes
APEX[69,70]				
Single bortezomib	333	43	15 CR/nCR	TTP 6.2m, OS 29.8m
High dose dexamethasone	336	18	2 CR/nCR	TTP 3.5m OS 23.7m
DOXIL-MMY-3001[71]				
Bortezomib + liposomal doxorubicin	324	44	13 CR/nCR 27 VGPR	TTP 9.3 m, PFS 9m, 15m OS76%
Single bortezomib	322	41	10 CR/nCR 19 VGPR	TTP 6.5m, PFS 6.5m, 15m OS 65%
MM-009[72]				
Lenalidomide + dexamet hasone	177	61	24 CR/nCR	TTP: 11.1 m OS 29.6 m
Dexamethasone	176	20	2 CR/nCR	TTP: 4.7 m OS 20.2 m
MM-010[73]				
Lenalidomide + dexamethasone	176	60	24 CR/nCR	TTP: 11.3 m OS not reached
Dexamethasone	175	24	5 CR/nCR	TTP 4.7m OS 20.6m
Palumbo et al[74]				
Bortezomib + liposomal doxorubicine + dexamethasone	64	67	9 CR/ 25 VGPF PR	1 year EFS 83% 1 year OS 90% 1 year EFS 16% 1 year OS 63%
Hussein et al[75]				
Liposomal doxorubicin, vincristine, dexamethasone, thalidomide	49	76	20 CR 45 VGPR	

ORR: overall response rate; CR: complete response; nCR: near complete response; VGPR: vary good partial response; PR: partial response; TTP: time to progression; OS: overall survival; EFS: event free survival.

Table 4. Differences in Definitions of good Responses in the most commonly used MM response criteria

	EBMT criteria18	IMWG uniform criteria19
sCR	No defined	• CR+ normal FLC ratio • Absence of clonal plasma cells by immunochemistry or flurescence
CR	• Absence of M-protein in serum and urine by immunofixation • Plasma cells <5% in bone marrow • No increase the number of lytic lesions • Disappearance of soft tissue plasmacytoma	
VGPR		• Serum and urine M protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M protein + urine M protein < 100mg/24 hours

sCR: stringent complete response; CR: complete response; VGPR: very good partial response.

Table 5. Sensitive rate of diagnostic and analytical techniques

Technique	Detection substance	Sensitivity rate	Reference
Bone marrow aspiration/biopsy	Cytomorphalogic assessment	<5% in bone marrow	18, 19
Serum/urine protein electrophoresis	Monoclonal proteins/light chains in the serum/urine	1-2 g/L	18, 19, 37-39
Serum/urine immunofixation	Monoclonal protein	150-500mg/L	18,19, 37, 39
Serum free light chain assay	Ratio of kappa/lambda light chains	<1mg/L	19, 37, 40
Immunohistochemistry/immunofluorore-scence	Quantitation of myeloma plasma cells in bone marrow via antibody-antigen interaction	10^{-2}-10^{-3}	19, 41
Immunophenotyping (multiparametric flow cytometry)	Automated cell-by-cell quantitation of myeloma plasma cells	10^{-4}	20, 39,
Rea-time quantitative polymerase chain reaction for IgH rearrangement	Patient-specific selected immunoglobulin heavy-chain genomic rearrangements	10^{-6}	22,42, 43
Magnetic resonance imaging	Identification of focal lesions in the bone marrow	0.5cm	44
Positron emission tomography	Identification of focal lesions in the bone marrow		23

from GEM05>65y trial (six cycles of bortezomib-melphalan-prednisolone versus bortezomib-thalidomide-prednisolone followed by maintenance with bortezomib-thalidomide versus bortezomib-prednisolone up to 3 years) also showed no significant survival advantage in sCR compared with those in CR, but patients with MFC showed significantly increased PFS and TTP compared with those in sCR or CR[21]. In a multivariate Cox regression analysis of PFS, only immunophenotypic response (IR) was an independent prognostic factor (relative risk, 4.1; 95% CI, 1.4 to 12.0; P=0.01).

Another analysis of patients treated in GEM2000 showed that patients who were MRD negative by fluorescence PCR had a better PFS than those remaining MRD positive (68% vs. 28%, p=0.001), with similar findings even in patients achieving immunofixation-negative CR (75% vs. 25%, p=0.002)[32]. Real-time PCR of immunoglobulin heavy-chain rearrangement is a more sensitive tool to detect residual tumors. One recent study from 12 Italian centers showed a better PFS in patients with a low tumor burden compared with patients with a high tumor burden. No recurrence was noted in patients achieving molecular remission (MR) after 42 months follow-up. According to the results from recent studies, lower residual tumor burden has better PFS and OS[22].

Bone marrow magnetic resonance imaging (MRI) has been demonstrated to be an effective technique for routine determination of disease burden in patients with MM[33], and use of MRI to detect focal lesions harboring viable monoclonal plasma cells may also improve the prognostic significance of CR[34]. F18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a powerful tool to investigate the role of tumor metabolic activity and its suppression by therapy for cancer survival. It has also been used to detect focal lesions in MM, and the number of focal lesions has been shown to be related to OS and event free survival (EFS). Complete FDG suppression in focal lesions before first transplantation has been shown to confer significantly better outcomes and is only opposed by gene expression profiling defined high risk status[23].

Discussion

The prognosis of MM is complex and influenced by multiple factors. According to multiple phase III and large phase II clinical trials, CR is an important prognostic factor at all stages of treatment, including with auto-HSCT and without auto-HSCT, both in first line treatment and refractory or relapse disease. A more stringent definition of CR is used in the IMWG uniform response criteria compared to the EBMT criteria. However, it is not clear whether the current response criteria are adequate for the analysis of OS, PFS, and TTP.

Recent studies analyzing the relationship between molecular remission by MFC and real-time RT-PCR, and prognosis in patients from clinical trials have shown that molecular remission has a higher impact factor than current response definitions of sCR or CR. This may be due to a greater sensitivity in the detection of residual tumors in those methods compared to the standard methods. In addition, a lesser amount of residual tumors will increase OS and PFS. One study showed that FDG-PET for focal lesion detection is another prognostic factor for MM treatment. Based on these observations, clinicians can use these techniques to monitor the depth of remission in their patients, as is routine in chronic myeloid leukemia (CML), and thereby make informed evidence-based decisions regarding ongoing or subsequent therapy[35,36]. It will also help make informed decisions as to whether the patients should undergo first or second transplantation as part of first-line therapy. However, more prospective studies using such sensitive tools to determine the prognosis under different front-line therapy with/without auto-HSCT and different treatments for relapse or refractory MM are needed.

The issue of patient management on relapse from a CR defined using sensitive assessment techniques must be considered. We should consider whether changes in status are of practical relevance regarding ongoing management. For example, changes from IFx-to IFx+or MRD-to MRD+by real-time RT-PCR or MFC requires initiating further treatment or changes to the current treatment. This indicates the need for more intensive follow-up to determine whether the patients are beginning to experience true clinical relapse or whether the findings represent temporary biochemical or molecular changes in disease status.

Nevertheless, highly sensitive techniques have limitations. Not all myeloma cells show the same immunophenotypic surface markers. Multi-parameter immunofluorescent analysis at diagnosis and after treatment should be considered to cover more than 90% of myeloma cells. For IgH-R analysis, up to 60% of patients showed that real-time qRT-PCR can be used at diagnosis and after treatment. Because of the high cost of personal specific detection tools such as IgH-R real time qRT-PCR, we suggest that it should be used at diagnosis and when achieving negative results in current detection techniques, such as IF.

In conclusion, CR is a meaningful, important clinical treatment goal in MM patients. A deeper response status detected by more sensitive methods such as MFC and real-time RT-PCR, to obtain better outcomes with longer PFS and OS, have been reported in recent studies. More prospective studies for prognosis and analysis of the more sensitive methods are needed to modify the current response criteria. Whether MRD status change, detected by MFC or real-time RT-PCR, can be a guide to initiate treatment or change the treatment plan requires further research to evaluate.

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多發性骨髓瘤的完全緩解：我們需要改變定義嗎？

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摘　要

多發性骨髓瘤是漿細胞 (一種 B 細胞) 不正常增生的腫瘤，其發生率在不同的國家從十萬分之一到十萬分之四不等，這可能是因爲在有些國家中的診斷率太低；多發性骨髓瘤目前的治療目標是放在延長疾病惡化的時間及整體存活率，近幾年，因診斷及偵測方法的進步，如用即時定量 PCR 檢測免疫球蛋白重鏈的重新排列、多分項的流體細胞移檢測表面抗原、基因微陣列晶片偵測甲基化、以及影像診斷如正子攝影，我們可以偵測較微量的殘存腫瘤細胞，有些近年來的研究顯示疾病在治療後達到分子檢查的緩解與疾病惡化時間與存活率有正向相關性。EBMT (European Group for Blood and Marrow Transplant) 及 IMWG (International Myeloma Working Group) uniform criteria 是目前評估多發性骨髓瘤治療反應的標準，但似乎對整體預後的預測不夠敏感。日後以更精確敏感的方法檢測治療效果，是達到長期良好的反應所必需的，也可使完全緩解的定義更爲精準。