Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma

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Acknowledgments: the authors would like to thank Jennifer Friend-Huizer (Pharma R&D Information Management, JJPRD, Titusville USA) for her help in performing an exhaustive literature search, Drs. Dixie-Lee Esseltine, Anthony Boral and Iain Webb for their critical review and An Van Eyken for excellent editorial assistance.

Manuscript received March 21, 2007.
Manuscript accepted July 20, 2007.

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ABSTRACT

There are a number of reports in literature data on the long-term outcomes of patients with multiple myeloma treated with high-dose therapy and autologous stem cell transplantation (HDT/SCT). While in general these data support the association between maximal tumor response and overall survival or progression-free survival after HDT/SCT, some trials have failed to find such correlation and there is no recent comprehensive literature analysis of this issue. We, therefore, performed a comprehensive literature review to identify prospective and retrospective studies on HDT/SCT in frontline multiple myeloma in which long-term outcomes were reported according to best tumor response observed. Following a prospectively defined search strategy we identified 21 studies (10 prospective and 11 retrospective studies) in which outcomes of 4,990 HDT/SCT patients according to their best tumor response were reported. The majority of these studies indicated a correlation between maximal response during or after HDT/SCT and long-term outcomes (overall survival and event-free/progression-free survival). The conclusions in individual studis report on the association between maximal response following induction therapy and long-term outcomes were more heterogeneous, possibly due to the low rate of complete response after standard induction therapy in each individual study. We, therefore, performed two types of meta-analyses, one based on the *p*-values reported for these associations in the individual studies, and one based on the primary response and outcome data provided in the individual studies. Both meta-analyses indicated highly significant associations between maximal response (complete response/near complete response/very good partial response) during or after HDT/SCT and long-term outcomes (overall survival and event-free/progression-free survival). Both meta-analyses also provided evidence of highly significant associations between maximal response following induction therapy and long-term outcomes (overall survival and event-free/progression-free survival).

Key words: long-term survival, progression-free survival, high-dose therapy, multiple myeloma.

Haematologica 2007; 92:1399-1406. DOI: 10.3324/haematol.11534

The ultimate goal of high-dose therapy and stem cell transplantation (HDT/SCT) in patients with newly diagnosed multiple myeloma is to maximize the chance of long-term survival. It would be expected in this setting that a complete tumor response would be important in achieving the goals of long-term disease-free and overall survival, and perhaps even cure. There are extensive literature data on HDT/SCT, both from prospective randomized studies and from retrospective case series, which report on long-term outcomes according to the best observed tumor response. While in general these data support the relationship between maximal response and overall survival, some trials have failed to find such a correlation. We performed a com-

prehensive literature search on this topic and report on our meta-analytic approach to the identified studies. This information is not only relevant for care of individual patients (e.g., decision to perform a second transplant), but also for the development of novel regimens as part of the HDT/SCT approach. As the median survival of patients following HDT/SCT is 5 to 6 years, mature survival results of large prospective studies are only published 9 to 13 years after initiation of the studies.[1–5] In order not to delay the recognition of improvements in the HDT/SCT approach, it is important to understand the value of shorter term end-points such as complete response (CR) rate or near-complete response (nCR) rate as early predictors of long-term benefit.

A complicating factor in a literature review is the presence of heterogeneity in the response criteria used in published trials (EBMT, ECOG, SWOG). A CR is generally defined as the absence of paraprotein on electrophoresis of serum and urine, disappearance of soft tissue plasmacytomas, with no evidence of progression in bone lesions, and in most cases with the documentation of less than 5% plasma cells in a bone marrow sample. If immunofixation (IF) tests are also performed on serum and urine, negative IF tests are required for CR, while a positive IF test in serum or urine leads to a nCR if all other criteria for CR are met. A very good partial response (VGPR) indicates a 90% or greater reduction in the paraprotein level. The focus of this literature review was to compare the long-term outcomes of patients with these response categories (CR/nCR/VGPR) to the long-term outcomes of patients with the other response categories.

Literature search

We followed published guidelines for medical literature reviews.[6-8] The medical literature was searched in the OVID database (Medline, Embase, Derwent Drug File, Biosis) without a data range limit until December 1 2006. The following search strategy was used: Multiple Myeloma.mp AND New* (within two words of) Diagnos*.mp AND (Autologous Transplant* or Bone Marrow Transplant* or Stem Cell Transplant* or High-dose Therapy).mp AND (Surviv* or Respons* or Remission or Outcom* or Event-free Surviv* or Progression-free surviv*).mp. The identified studies included in this review are both prospective and retrospective in design, and were published in peer-reviewed journals and/or presented at international hematology conferences.

In our selection of articles, we focused on the presence of reported long-term outcome data (overall survival, progression-free or event-free survival) per response subgroup and/or on the presence of reported *p*-values in the association analysis between response and long-term outcomes. Unfortunately for some large studies on HDT/SCT such detailed data per response category were not available and therefore could not be incorporated. None of the selected studies addressed a research question related to a commercial interest of the authors' employer nor were any studies de-selected due to a commercial interest. Therefore this work does not constitute a conflict-of-interest. The selection and data extraction was performed by the first author and checked for accuracy by two co-authors (AC, WD).

Statistical analysis

Statistical methods used in identified individual studies

Most studies utilized certain analytical approaches to remove the *time-to-response* bias, e.g., Cox's model with time-dependent covariate, and landmark analyses, while several studies did not indicate what statistical method was used in such analyses.

Intrinsic variations in such analyses were noted in: (1) varying definitions of response criteria and long-term outcomes (time to disease progression [TTP], progression-free survival [PFS], event-free survival [EFS], relapse-free survival [RFS], etc.); (2) analytical approach (e.g., Cox's model with time-dependent covariates [univariate or multivariate]); and (3) response categories considered in such analyses (e.g., CR vs PR, or CR/VGPR vs PR or no response).

Meta-analytical methods

The aim of our meta-analyses was to explore the association between long-term outcomes and CR (and/or nCR and/or VGPR) in HDT/SCT-treated patients. A fixed-effects meta-analytical model was used.

All *p* values presented in the publications testing comparisons of long-term outcomes between patients achieving CR (and/or nCR and/or VGPR) and other response categories were directly included in the meta-analyses. If there was no such comparison reported in the publication, but the primary data (e.g., estimates of median time to event, or event-free rate at a specific time point) on overall survival or TTP (or PFS, EFS, etc.) were available for patients with CR (and/or nCR and/or VGPR) and other groups of response categories, we performed the Cochran Armitage's trend test to compare the reported or estimated event-free probabilities at a specific time-point between ordinal response categories. The meta-analyses were then performed using Fisher's combination test based on ensuing *p*-values from each study. To assess potential publication bias, funnel plots were prepared in which the standardized test statistics were plotted against the effective sample sizes. Publication bias would be suspected when part of the plot was sparse or empty. The test proposed by Begg and Mazumdar[9] was used to test for publication bias. A significant finding would suggest the existence of publication bias.

Two sensitivity analyses were conducted as follows. In one analysis, only the reported *p*-values from each individual study were utilized in the meta-analysis using Fisher's combination test. In the other, a Cochran-Armitage trend test was performed (one-sided) for each

individual study. The combined *p*-value for the association was then obtained from the weighted Z test statistic (two-sided) with the weight based on the effective sample sizes of the individual studies.

Results

Using the search strategy outlined above, we identified 273 citations which were hand-searched for the presence of reported long-term outcome data per response subgroup and/or for the presence of reported *p* values in the correlation analysis between response and long-term outcomes. Out of the 273 citations, 21 reports could be identified as independent data sets for which such outcome data were reported. These 21 reports consist of ten prospective studies (four single HDT/SCT studies and six tandem HDT/SCT studies; six phase III and four phase II studies) and 11 retrospective series. The total number of HDT/SCT patients reported in these studies is 4990, comprising 2991 patients in the prospective studies and 1999 patients in the retrospective series.

Reported associations between maximal response and long-term outcomes

The two phase III studies which first proved the survival benefit of a single HDT/SCT over conventional dose therapy in frontline multiple myeloma (IFM-90 and MRC VII) also provided initial evidence that maximal response was correlated with survival (Table 1).[3;10] In two other single transplant studies, NMSG5/94 and GMA, patients in CR after HDT/SCT had a numerically longer survival than patients with less than a CR but these differences were not statistically significant.[5,11] In studies evaluating tandem transplants, the importance of obtaining a CR or nCR was further confirmed (Table 1). Among the patients treated with Total Therapy I, those who achieved a CR after the first transplant had longer EFS and overall survival as compared with patients with only a PR.[4] Among the patients treated with Total Therapy II, EFS and overall survival were significantly longer for those who had a CR than for those who had a PR or no response.[12] These observations were further confirmed by three IFM studies (IFM 94-02, IFM 99-02, IFM 99-04/99-03) and the Italian Bologna 2002 study showing highly significant correlations between obtaining at least a VGPR after the second transplant and overall survival or EFS.[2,13,14] Additional analyses were reported on the importance of the timing of the CR. In Total Therapy I, the duration of CR was significantly longer in patients with early onset of CR.[4] Patients with early CR had a better prognosis than patients with late CR if there was an abnormal baseline karyotype, while the time to CR did not seem to influence the EFS and overall survival in case of normal cytogenetics.[15] In the IFM 94-02 trial, patients who had already obtained a CR/VGPR after one transplant (CR1/VGPR1) did not benefit significantly from a second transplant in terms of overall survival.[2]

The importance of CR or VGPR following HDT was confirmed in most, but not all, retrospective series (Table 2). The correlations between CR following HDT and overall survival were reported in eight studies, five of which showed statistical significance,[16-20] while such a correlation was not reported in three other series.[21-23] The correlations between CR following HDT and EFS/PFS were reported in nine studies, seven of which showed statistical significance,[16-20,23,24] and no significant correlation was reported in the same two other series.[21,22]

Reported associations between pre-HDT/SCT response and long-term outcomes

Several studies specifically reported on the associations between CR pre-HDT/SCT and long-term outcomes. These associations are more difficult to interpret as the CR/nCR/VGPR rate following induction is generally low (5-15%) and therefore the sample size may be too small to show a statistically significant association. A statistically significant association between CR after induction therapy and EFS/PFS was reported in five of the nine studies in which such an analysis was provided[20,21,24-26] with a non-significant trend in one other study,[19] while such a correlation was reported absent in three other studies.[14,15,22] A statistically significant correlation between CR after induction therapy and overall survival was reported in three studies[18,24,25] with a non-significant trend in one other study[20] while such a correlation was again reported absent in four studies.[14,19,21,22] In two other studies, the response to induction therapy (pre-transplant tumor burden) was identified as an independent determinant of the probability of obtaining a CR following transplantation.[16,17] The importance of a CR, whether obtained without or after an HDT/SCT procedure, was further substantiated by reports from Alexanian *et al.* and Blade *et al.*[27,28] In a matched control analysis, the survival of patients with disease converted from PR post-induction to CR post HDT/SCT was superior to the survival of patients with persisting PR despite intensive therapy.[27] On the other hand, the RFS and overall survival of patients converted from PR to CR by intensive therapy was the same as for a matched control patient population with CR to standard-dose chemotherapy who never received HDT/SCT.

Meta-analysis approach

In order to further assess the association between response and long-term outcomes, we performed a meta-analysis based on the results reported in the 21 published studies described above. For long-term outcomes, two sets of parameters were tested separately: overall survival (Table 3) and the time to progression-related events (TTP, PFS, EFS, RFS) (Table 4). For response, two parameters were tested separately: maximal response after the induction/HDT/SCT regimen and maximal post-induction pre-HDT/SCT response. The associations between maximal response and overall survival and between maximal response and time to progression events were highly sta-

Table 1. Efficacy outcomes in prospective studies on HDT/SCT for newly diagnosed multiple myeloma.

Study	*Pts (N)*	*Response (post-induction)*	*Response rate 1 (post-HDT1)*	*Response rate 2 (post-HDT2)*	*Event-free survival/ Progression-free survival*	*Overall survival*
Single transplant						
IFM-90[1,10]	100		CR1:22% VGPR1:16% PR1:43% <PR1:19%			5 y OS CR1/VGPR1:72% 5 y OS PR1:39% 5 y OS <PR1:0%
MRC VII[3]	201		CR1:44% PR1:42% MR1:3%			Med OS CR1 88.6 m Med OS PR1 39.8 m Med OS MR1 25.6 m
NMSG 5/94[11]	247	CR:13% PR:60% MR:8%	CR1:43% PR1:47% MR1:8%		Med EFS CR1 40 m Med EFS <CR1 27 m	Med OS CR1 71 m Med OS <CR1: 64 m
GMA[5]	94		CR1/MRD1:36% PR1:26% MR1:7.5%			Med OS CR1/MRD1 59 m Med OS <CR1/MRD1 40.5 m
Double transplant						
TT1[4]	231	CR:15% PR:50%	CR1:26% PR1:49%	CR2 41% PR2:42%	Med EFS CR1 78+ m Med EFS PR1 52 m	Med OS CR1 80+ m Med OS PR1 68 m
TT2[12;15]	668	CR:16%[15] nCR:19% PR:19% <PR:46%	CR1:30%[15] nCR1:28% PR1:20% <PR1:22%	CR2:56%[15] nCR2:24% PR2:12% <PR2:9%	PR to nCR/CR1 4-y EFS 70%[15] PR to PR1 4-y EFS 26%	CR to CR1 4 y OS 70%[1516] PR,/nCR to CR1 4-y OS 62% <PR to CR1 4 y OS 50%
IFM 94-02[2]	399	CR/VGPR: 12%	CR/VGPR1: 42% PR1: 42%	CR/VGPR2:50% PR2:38%		
IFM 99-02[14] IFM 99-04/99-03	849	CR:4% VGPR:12% PR:49%		CR2:33% VGPR2:22% PR2:36%	Med EFS CR2 42 m Med EFS VGPR2 36 m Med EFS PR2 32 m Med EFS <PR2 24 m	4-y OS CR2:80% 4-y OS VGPR2:76% 4-y OS PR2:67% 4-y OS <PR2:65%
Bologna 2002[13]	142	CR:15%	CR1:39% nCR:4% VGPR:13%	CR2:54% nCR1:8%	nCR2:7%	
Barbui *et al.*[26]	60				3-y EFS CR 86% EFS <CR 44%	

CR: complete response; EFS: event-free survival; HDT/SCT: high dose chemotherapy/stem cell transplant; IFM: InterGroupe Francophone de Myelome; MR: minor response (≥25% decrease in serum paraprotein and/or a ≥50% or ≥25% decrease in urine paraprotein); MRC: Medical Research Council; MRD: minimal residual disease; nCR: near complete response; NR: no response; OS: overall survival; PFS: progression-free survival; PR: partial response (≥50% decrease in serum paraprotein and/or ≥90% decrease in urine paraprotein); TT: Total Therapy; VGPR: very good partial response (≥90% decrease in serum paraprotein). CR1: complete response after first HDT/SCT; CR2: complete response after second HDT/SCT, m: month, y: year; med: median.

tistically significant for both the prospective (p<0.00001) and the retrospective (p<0.00001) studies (Tables 3 and 4). The associations between pre-transplant response and overall survival and between pre-transplant-response and time-to-progression events also appeared highly statistically significant (p=0.0015 and p<0.00001, respectively; Tables 3 and 4). To assess potential publication bias, funnel plots were generated in which the standardized test statistics were plotted against the effective sample sizes (*data not shown*). The shape of the plots, while not perfectly symmetric, did not show markedly asymmetric patterns. With all studies included, the Begg and Mazumdar test yielded a p value of 0.1063, suggesting weak evidence of publication bias. With prospective studies only, the test showed little evidence of publication bias (p=0.6002).

To validate the findings, we also performed a sensitivity analysis using a meta-analysis model including only the primary response and survival/progression data (*data not shown*). Primary data on at least some of these parameters were reported in 18 out of the 21 publications. These sensitivity analyses confirmed the conclusions from Tables 3 and 4. The association between maximal

Table 2. Efficacy outcomes in retrospective case series of HDT/SCT in newly diagnosed multiple myeloma.

Study	*Pts (N)*	*Response Rate (post-induction)*	*Response rate1 (post-HDT1)*	*Response rate2 (post-HDT2)*	*Event-free survival/ Progression-free survival*	*Overall survival*
Nadal[16]	59	CR: 8% PR: 70% MR: 22%	CR1: 37%		Med EFS CR1 47 m Med EFS <CR1 36 m	Med OS CR1 NR Med OS <CR1 60 m
Krecji[19]	181	CR: 7% PR: 62% MR: 18% NR: 12%	CR1: 30% PR1/VGPR1: 65%/35% MR1: 4% NR1: 1%		Med TTP CR1/VGPR1 44.6 m Med TTP <VGPR1:23.8 mo	Med OS CR1/VGPR1 87 m Med OS <VGPR1 66 m
Lahuerta[17]	344		CR1: 24% nCR1: 19% VGPR1: 16% PR1: 33%		5 y EFS CR1 35% 5 y EFS nCR1 21% 5 y EFS VGPR1 27% 5 y EFS PR1 15%	5 y OS CR1 72% 5 y OS nCR1 48% 5 y OS VGPR1 42% 5 y OS PR1 41%
Alvares[18]	383	CR: 15% PR: 51% NR: 26%	CR1: 50% PR1: 10% NR1: 34%		Med TTP CR 3.8 y Med TTP PR/NR1 1.87 y Med OS CR/PR 6.4 y	Med OS NR 4.1 y Med OS CR1 7.4 y Med OS PR/NR1 5.3 y
Galli[21]	110	CR: 15% CR/VGPR: 26% PR: 57% PR/NR: 74%	CR1: 39% PR/NR1: 48%	CR2: 46% PR/NR2: 25%	5 y EFS CR 65% 5 y EFS CR/VGPR 54% 5 y EFS PR/NR 24% 5 y EFS CR1 32% 5 y EFS PR/NR1 30% 5 y EFS CR2 33% 5 y EFS PR/NR2 34%	5 y OS CR 63% 5 y OS CR/VGPR 63% 5 y OS PR/NR 47% 5 y OS CR1 50% 5 y OS PR/NR1 58% 5 y OS CR2 59% 5 y OS PR/NR2 63%
Alexanian[27]	68	CR: 6%	CR1: 37%		PR to CR1 med RFS: 4.1 y PR to PR1 med RFS: 2.3 y	PR to CR1 med OS 8.3 y PR to PR1 median OS 5 y
O'Shea[20]	211	CR: 5.2% PR: 71.2% MR: 10.4%	CR1: 16% PR1: 68% MR1: 13%		Med EFS CR1 59 m Med EFS PR1 22 m Med EFS MR1 9 m	Med OS CR1 NR Med OS PR1 47 m Med OS MR1 34 m
Davies.[22]	96	CR 18% PR 70% MR 9%	CR1 53% PR1 47%		Med PFS CR1 49.4 m Med PFS PR1 41.4 m	5-y OS CR1 58% 5-y OS PR1 64%
Majolino[25]	290	CR 19.7% PR 66.2%	CR1 40% PR1 50%			
Terpos [23]	127	CR: 6% PR: 73%	CR1: 15% PR1: 81%		Med PFS CR1 31 m Med PFS PR1 16.3 m Med PFS CR/PR 24 m Med PFS MR/NR 18.4 m	3-y OS CR1 77% 3-y OS PR1 69% Med OS CR/PR 50.2 m Med OS MR/NR 58.9 m
Bjorkstrand[24]	130	CR: 12% PR: 56%	CR1: 47% PR1: 47%			

ASCT: autologous stem cell transplant; CR: complete response; EFS: event-free survival; HDT: high-dose chemotherapy; HDT/SCT: high dose chemotherapy/stem cell transplant; MM: multiple myeloma; MR: minor response (≥25% decrease in serum paraprotein and/or a ≥50% or ≥25% decrease in urine paraprotein); nCR: near complete response; NR: no response; OS: overall survival; PFS: progression-free survival; PR: partial response (≥50% decrease in serum paraprotein and/or ≥90% decrease in urine paraprotein); RFS: relapse-free survival; TTP: time to progression; VGPR: very good partial response (≥90% decrease in serum paraprotein); CR1: complete response after first HDT/SCT; CR2: complete response after second HDT/SCT; m: month; y: year; med: median.

response and overall survival was highly significant (p<0.00001; data on 3,007 patients), as was the association between maximal response and time to progression events (p<0.00001; data on 2,683 patients). The highly significant associations between maximal pre-transplant response and overall survival (p=0.0027; data on 898 patients) and between maximal pre-transplant response and time to progression events (p=0.0001; data on 710 patients) were also confirmed.

Discussion

One would expect that obtaining a CR during cancer therapy would be of paramount importance to achieve the goals of a prolonged disease-free period, prolonged survival, or cure. After all, the disappearance of a tumor is the best result one can expect from treatment, and a *conditio sine qua non* for potential cure. It is apparent from this literature review that many, but not all, individual

Table 3. Association between maximal response or pre-transplant response and overall survival in patients with newly diagnosed multiple myeloma treated with HDT.

Study	Maximal response		Pre-transplant response	
	Comparison	p value	Comparison	p value
Prospective				
IFM90[1;10]	CR/VGPR vs. PR vs. Other	<0.00001[a]		
MRC VII[3]	CR vs. PR vs. MR	0.00002[a]		
TT1*[4]	CR vs. PR	0.2496[a]		
TT2[12;15]	CR vs. PR/NR	<0.05[b1]		
IFM94-02[2]	Maximal response	<0.001[b1]		
IFM99C[14]	CR/VGPR vs. PR	<0.0000[1f]	CR/VGPR vs. PR	0.98[f]
NMSG 5/94[11]	CR vs. PR/NR	0.38[c]		
Bologna[13]	VGPR or better vs. Other	0.002[d]		
GMA[5]	CR/MRD vs. Other	0.22[e]		
Combined		<0.00001**		
Retrospective				
Nadal[16]	CR vs. No CR	0.006[e]		
Krejci[19]	CR vs. No CR	<0.001[f]	CR/VGPR vs. Other	0.876[f]
Lahuerta[17]	CR IF- vs. nCR/PR vs NR	<0.00001[b2]		
Alvares[18]	CR vs. No CR	0.023[f]	Response vs. No Response	0.0085[f]
Galli[21]	CR vs. PR/NR	0.7985[a]	CR vs. No CR	0.3139[e]
Alexanian[27]	PR to CR after HDT vs. PR after HDT	0.03[e]		
O'Shea[20]	CR vs. PR vs. MR	0.0003[e]	CR vs. PR vs. MR	0.06[e]
Davies[22]	CR vs. PR	>0.05[b2]	Response vs. No Response	0.4[b2]
Bjorkstrand[24]	CR or PR vs. NR	0.001e	Response vs. No Response	0.0009[b2]
Terpos[23]	CR vs. PR	0.65[e]	CR/PR vs. Other	0.98[e]
Majolino[25]			CR/PR vs. NR	0.026[b2]
Combined		<0.00001**		0.0006**
Overall		<0.00001**		0.0015**

*[a]Cochran-Armitage's trend test comparing the estimated 5-year survival rates, [b1]Cox's model with time-varying covariate; [b2]Cox's model; [c]multivariate landmark analysis; [d]multivariate analysis; [e]log-rank test; [f]not specified. *The article reported a p value of 0.02 assessing the effect on overall survival by attaining CR in a timely fashion. **Fisher's combination test is used. A p value reported as "<0.xxx" is interpreted as 0.xxx-0.0001. For instance, a p value of <0.05 is interpreted as 0.049, whereas 0.0009 is used for "<0.001". A p value reported as ">0.05" is interpreted as 0.9999.*

studies provide evidence of an association between a CR during or after HDT/SCT in frontline multiple myeloma and long-term survival or progression-free survival. Several factors may have contributed to this observed heterogeneity.

First, there has been a historical heterogeneity in the definition of the CR end-point in multiple myeloma. For this meta-analysis, the entities of CR/nCR/CGPR were grouped and compared with the other response categories. However, one may hypothesize that these are biologically different response categories. Furthermore, more rigorous methods currently exist to assess CR. A novel *stringent CR (sCR)* category has been defined by the IMWG, which, besides a normalization of the free κ/λ ratio in serum, also requires immunophenotypic normalization of the κ/λ ratio in the bone marrow. Others have argued that a random bone marrow examination has a risk to miss focal lesions harboring viable malignant plasma cells and that alternative techniques, such as magnetic resonance imaging or positron emission tomography, should be applied to determine true CR.[29, 30] One may expect that use of these additional technologies will have the potential to identify more rigorously characterized complete responses with favorable survival implications. However, the performance of these tests, including the estimation of a false positive rate, still needs to be determined.

Another source of heterogeneity in the *p*-values reported in individual studies may have been the limited sample size of some of the studies and especially the limited number of complete responders within each study. This is especially true for the assessment of long-term outcomes of complete responders following induction therapy, which was generally limited to 5-15% of the patient population. In order to overcome this concern of limited sample size, we performed two types of meta-analyses both indicating highly significant associations between CR and long-term outcomes. There are several methodological limitations of this meta-analysis approach: (i) first, while we attempted to perform a comprehensive literature search using a pre-defined and reproducible search strategy, it cannot be excluded that some publicly available information on HDT/SCT outcomes was missed; (ii) second, these meta-analyses do not incorporate all studies performed on HDT/SCT in multiple myeloma but only those which we could identify as reporting long-term outcome data per response subgroup and/or *p*-values of association analyses between response and long-term outcomes. A reporting bias can not, therefore, be excluded, even though funnel plots and

Table 4. Association between maximal response or pre-transplant response and EFS/PFS/RFS/TTP in patients with newly diagnosed multiple myeloma treated with HDT.

Study	End point	Maximal response		Pre-transplant response	
		Comparison	p value	Comparison	p value
Prospective					
TT1[4]	EFS	Attaining CR in a timely fashion	0.02[b1]		
TT2 [12;15]	EFS	CR vs. PR/NR	<0.05* [b1]	CR vs. PR/nCR vs. NR with CR post HDT	0.47[c]
NMSG 5/94[11]	PFS	CR vs. PR/NR	0.02[c]		
IFM99C[14]	EFS	CR/VGPR vs. PR	0.0007[f]	CR/VGPR vs. PR	0.39[f]
Bologna[14]	EFS	VGPR or better vs. Other	<0.001[d]		
GMA[5]	EFS	CR/MRD vs. Other	0.22[e]		
Barbui[26]	TTP			CR vs. No CR	0.003[b1]
Combined			<0.00001**		0.0202**
Retrospective					
Nadal[16]	EFS	CR vs. no CR	0.023[e]		
Krejci[19]	TTP	CR vs. No CR	<0.001[f]	CR/VGPR vs. Other	0.077[f]
Lahuerta[17]	EFS	CR IF- vs. nCR/PR vs. NR	<0.00001[b2]		
Alvares[18]	TTP	CR vs. No CR	0.0001[f]		
Alexanian[27]	RFS	PR to CR after HDT vs. PR after HDT	0.26[e]		
O'Shea[20]	EFS	CR vs. PR vs. MR	<0.0001[e]	CR vs. PR vs. MR	<0.0001[e]
Galli[21]	EFS	CR vs. PR/NR	0.4017[a]	CR vs. No CR	0.025[e]
Davies[22]	PFS	CR vs. PR	0.26[b2]	Response vs. No Response	0.5[b2:]
Bjorkstrand[24]	PFS	CR vs. No CR	0.03[b2]	Response vs. No Response	0.006[b2]
Majolino[25]	EFS			CR/PR vs. NR	0.006[b2]
Terpos[23]	PFS	CR vs. PR	0.009[e]	CR/PR vs. Other	0.41[e]
Combined			<0.00001**		<0.00001**
Overall**			<0.00001**		<0.00001**

*[a]Cochran-Armitage's trend test comparing the estimated 5-year survival rates, [b1]Cox's model with time-varying covariate; [b2]Cox's model; [c]Landmark analysis; [d]multivariate analysis; [e]log-rank test; [f]not specified. *Tricot (2006) reported a p value of 0.003 comparing EFS between those who improved from PR or nCR before HDT1 to CR versus those who remained at CR after HDT. **Fisher's combination test is used. A p value reported as "<0.xxx" is interpreted as 0.xxx-0.0001. For instance, a p value of <0.05 is interpreted as 0.049, whereas 0.0009 is used for "<0.001".*

Begg's test were performed and suggested weak or little evidence of publication bias. However, we would like to stress that all identified data were incorporated in the meta-analyses regardless of whether they supported or contradicted the association between response and long-term outcomes; (iii) third, the information available in publications is always limited. Besides heterogeneity in the CR assessment there was also some heterogeneity in the definitions of the time-to-progression events and in the reported method utilized to analyze the association. The meta-analyses would be more robust if the primary data of the different databases on HDT/SCT trials from the different cooperative groups and academic institutions could be merged and analyzed using the same parameter definitions across all trials. This may be a valuable avenue for future research; (iv) fourth, the interpretation of subgroup outcomes may change with new insights into disease biology. It has been argued that the survival implications of obtaining a CR are different in high-risk or low-risk disease and depends on parameters such as cytogenetic abnormalities and proliferation index. Such information is often lacking in historical studies and could not, therefore, be included in this meta-analysis.

Despite these methodological limitations the conclusions of the two meta-analyses were very consistent and supported the importance of obtaining a CR during the HDT/SCT approach (whether during induction or after the first or second HDT/SCT). We would like to point out that these conclusions should not be extrapolated to the frontline non-transplant approach in an elderly patient population. Studies on conventional dose chemotherapy in elderly patients were not included in this review and a previous meta-analysis came to a negative conclusion on the association between response and survival in non-transplant patients.[31] Future trials with novel agents, both in the non-transplant and transplant setting, are expected to shed further light on the importance of CR and the chances of long-term benefit for newly diagnosed myeloma patients.

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