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Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System (IPSS-R)

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-SCT) represents the only curative treatment for patients with myelodysplastic syndrome (MDS), but involves non-negligible morbidity and mortality. Crucial questions in clinical decision making include the definition of optimal timing of the procedure and the benefit of cytoreduction before transplant in high risk patients. We carried out a decision analysis on 1728 MDS who received supportive care, transplantation or hypomethylating agents (HMAs). Risk assessment was based on the revised International Prognostic Scoring System (IPSS-R). We used a continuous-time multistate Markov model to describe the natural history of disease and evaluate the effect of different treatment policies on survival. Life expectancy increased when transplantation was delayed from the initial stages to intermediate IPSS-R risk (gain of life expectancy 5.3, 4.7 and 2.8 years for patients aged ≤55, 60 and 65 years, respectively), and then decreased for higher risks. Modelling decision analysis on IPSS-R vs. original IPSS changed transplantation policy in 29% of patients, resulting in a 2-year gain in life expectancy. In advanced stages, HMAs given before transplant is associated with a 2-year gain of life expectancy, especially in older patients. These results provide a preliminary evidence to maximize the effectiveness of allo-SCT in MDS.

Keywords

myelodysplastic syndromes; transplantation; decision analysis; prognostic scores

Introduction

Myelodysplastic syndromes (MDS) are heterogeneous disorders that range from conditions with a near-normal life expectancy to forms approaching AML.1,2 A risk-adapted treatment strategy is mandatory, and the definition of individual risk requires the use of prognostic systems.3,4 In 1997 the International Prognostic Scoring System (IPSS) has been developed and become a benchmark for clinical trials and decision making.5 Nonetheless, a not negligible heterogeneity was observed in IPSS subgroups, in particular in patients classified in low and intermediate-1 risk categories. Recently, the International Working Group for Prognosis in MDS (IWG-PM) revised the IPSS.6 On the basis of a large data set that allowed the prognostic value of even less frequent karyotypic abnormalities to be estimated, 5 cytogenetic risk groups were determined representing the basis for the revised IPSS (IPSS-R), together with refined categories for bone marrow blasts and peripheral blood cytopenias. IPSS-R improved the capability to capture prognostic information in untreated MDS (where it identifies five risk groups compared to the four major prognostic categories that are present in the IPSS) as well as in patients receiving disease modifying treatments.7,8

The only curative treatment for MDS patients is allogeneic stem cell transplantation (allo-SCT) which is considered as a conventional therapeutic option until the age of 65-70 in eligible patients.9–12 Its efficacy, however, is considerably limited by morbidity and mortality, resulting in a long-term survival rate of about 30%.12,13

Several issues must be taken into account when considering allo-SCT and evaluating its benefits in the individual patient with MDS. A crucial question is timing of transplant procedure. A number of studies have shown that advanced disease stage at transplantation is associated with inferior overall survival.10–13 However, patients at early stages may experience long periods with stable disease after diagnosis, and the risks of morbidity and mortality related to allo-SCT would be unacceptably high for many of them.14 A previous decision analysis by the International Bone Marrow Transplant Registry (IBMTR) concluded that for patients with low and intermediate-1 IPSS-risk delayed transplantation offered optimal survival benefit.15 This study has substantially influenced clinical practice despite a number of intrinsic limitations. In particular, the IBMTR analysis considered patients at the time of MDS diagnosis, ignoring changes in their disease status that frequently occur before transplantation or leukemic evolution and significantly affect clinical outcome.

In patients with advanced disease, in which immediate transplantation is clearly associated with survival advantage, a crucial issue is whether performing cytoreductive therapy before allo-SCT. The achievement of complete remission improves post-transplantation outcome in high risk patients. 11,16,17 However, significant concerns about chemotherapy (especially AML-like chemotherapy) include low response rate and risk of long-lasting myelosuppression and organ toxicities, possibly affecting the eligibility to the transplant procedure.18

Hypomethylating agents (HMAs) have been found to be active in MDS, with a good toxicity profile compared with induction chemotherapy, and may therefore be of interest if used before transplantation.19–21

In this study we carried out an *ad hoc* decision analysis to address these issues. Decision analysis is a technique which allows to to measure the consequences of many strategies (treatment policies), under different conditions (disease status) and is used to address clinical relevant questions in the absence of evidence form randomized studies. Markov models are frequently used in decision analysis to stratify the natural history of a disease in different states.22–24

We analyzed 1728 MDS patients. We used a continuous time multistate Markov model to describe the natural history of disease according to IPSS-R risk categories. We specifically aimed: i) to evaluate the effect of allo-SCT on survival under different transplantation policies in patients with early disease stage, and ii) to evaluate the possible gain of life expectancy by using HMAs before transplantation in patients with advanced disease

Subjects and Methods

Patient population

These investigations were approved by the Ethics Committee of the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy and GITMO. All procedures were carried out in accordance with the ethical standards of the Declaration of Helsinki.

We analyzed different cohorts of MDS patients. The first cohort included 961 patients diagnosed with MDS according to WHO criteria25 at the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2010. The second cohort included 489 undergoing allo-SCT for primary MDS or AML evolved from MDS between 1997 and 2010, and reported to the GITMO registry. Secondary AML was included in this analysis since this condition is very close to RAEB-2, and not infrequently difficult to be distinguished from this latter condition. Most of these patients with AML evolved from MDS had the condition previously defined as refractory anemia with excess of blasts in transformation (RAEB-t), characterized by 20–29% blasts in the bone marrow. Different conditioning regimens and different donor types were used. Disease-related risk was evaluated by using IPSS-R. In the Pavia cohort, patients were essentially treated with best supportive care and regularly followed-up, and this allowed clinical data and disease staging to be monitored longitudinally. In the GITMO cohort, all clinical variables were analyzed at the time of transplantation in patients undergoing allo-SCT upfront, and at the time of remission-induction chemotherapy in those receiving treatment before allo-SCT. The effect of treatment with hypomethylating agents administered before transplantation was obtained from an analysis of the results of two studies including 278 patients treated with azacitidine. 19,26 (Table 1)

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Decision strategy

We adopted a continuous-time, multistate Markov approach to model the course of the disease in MDS patients.27 We estimated expected survival under different treatment policies where the IPSS-R prognostic score is used to determine timing of allo-SCT. In high risk patients each policy was in addition be modified by treatment with HMAs performed before transplant.

A multistate model describes how an individual moves between a series of states in time. Markov models are multistate models based on Markov processes, that is, stochastic processes with the property that the probability of moving to a particular state in the future only depends on this state and not on past states. Further information on Markov models is reported in Supplemental File 1. A continuous-time Markov model was used to estimate the risk of progression from each disease state to the next one. We fitted a model based on IPSS-R risk. (Figure 1). Each risk category was represented by a state in the model, and death was considered as absorbing state, that is, a state in which transitions to other states are not allowed. Transitions were allowed from any IPSS-R to the next one, to AML and to death. Transition intensity, that is, the instantaneous risk of moving to another state, was then estimated for each possible transition between states.

Allo-SCT and treatment with HMAs were modeled as a categorical time-dependent covariates, to allow for excess of mortality due to transplant-related causes. The effect of allo-SCT (alone or with HMAs) on mortality in each disease state was estimated as a hazard ratio (HR) with respect to the “no allo-SCT” category. Since allo-SCT does not represent an option for very low IPSS-R risk patients, the HRs for transplantation in this state were not modeled. A more detailed technical description of the models is reported in supplemental File 1.

The expected survival, that is, the expected time spent by a patient in the model before reaching the absorbing state (death), under different transplant policies was calculated algebraically for the fitted Markov model. These calculations were validated by microsimulation, and a confidence interval was obtained by bootstrap resampling.

The effect of treatment with hypomethylating agents is obtained from an analysis of the results of two studies.19,26 To estimate expected survival in the periods when HMAs are given, the equivalent HMAs-free survival times (estimated from the cohort data) are multiplied by the ratio of expected survival time.

Life expectancy was also estimated accounting for quality of life (QoL), based on quality-adjusted life years (QALY).28,29 We made QoL adjustments by incorporating utilities into estimation of life expectancy. Utilities are numerical representations of the perceived value of a given health state and are expressed as values between 0 (a health state equivalent to being dead) and 1 (perfect health). To account for worsening of QoL with disease progression or transplant-related complications, we defined plausible utilities using previously published data. Analyses with and without adjustment for QoL were performed independently.

The Markov models were implemented with the *msm* package for R (R Development Core Team 2009) 30 freely available from http://CRAN.R-project.org/package5msm.

Results

Outcome of MDS patients classified according to IPSS-R

In the Pavia cohort, IPSS-R significantly stratified the probability of survival of MDS patients (P<.001) (Figure 2A). The cumulative incidences of disease progression and of death for each IPSS-R category are reported in Supplemental Table 1.

Compared to the Pavia cohort, the GITMO cohort was younger (P<.001), and had a higher proportion of cases with more advanced IPSS-R (P<.001). IPSS-R significantly stratified post-transplantation survival (P<.001) (Figure 2B). In an exploratory multivariate survival analysis, type of donor (HLA-sibling or MUD) and of conditioning (standard or reduced-intensity) did not significantly affect post-transplant survival. (Supplemental Table 2) Therefore, all the above types of donor and conditioning regimen were included in the subsequent decision analysis. The HMAs cohort included a higher proportion of cases with more advanced disease compared to the Pavia cohort (P<.001), while no significant difference was found on demographic factors; compared to the GITMO cohort, the HMAs cohort was older (P<.001).

IPSS-R based transplantation policies

We fitted a model of the clinical course of MDS in which patients were stratified according to IPSS-R. As a first step we analysed the goodness of fit of the IPSS-R-based Markov model as compared to the observed survival. No major lack of fit was highlighted in either model (not shown).

We then focused on the effect of allo-SCT on survival. In lower IPSS-R risk categories, the HRs after transplantation were very high, due to the risk of NRM, as compared to a relatively low mortality in non transplanted patients. This was not observed in higher IPSS-R risk categories, where mortality in non transplanted subjects is much higher. The HRs associated with transplantation are reported in Supplemental Table 1. In order to assess the optimal transplantation timing, the expected survival since diagnosis according to the IPSS-R model was calculated for different transplant policies.

We analysed two different treatment policies, as follows.

Policy A: perform transplant in state 2 (low IPSS-R) at t years since entering the state (t ranging from 0 to 5), or immediately in case of disease progression before the planned delay time t.

Policy B: do not transplant while in state 2; perform transplant in state 3 (intermediate-IPSS-R) at t years since entering the state (t ranging from 0 to 5), or immediately in case of disease progression before the planned delay time t.

Each policy was evaluated for a set of different ages at diagnosis (between 30 and 70, with 5-year intervals). Under all policies, the patient lost eligibility to transplantation at 70 years

of age. According to the model, a patient with a low IPSS-R risk is expected to spend 3.66 years in this low risk group, 2.36 years in the intermediate risk group, and 1.58 years in the high risk group. The cumulative incidence of progression from low to a higher IPSS-R risk was 27% at 3 years, and that form intermediate to a higher risk was 39%.

Life expectancy (evaluated since time of diagnosis) under different treatment policies is reported in Table 2. Overall, expected survival times from diagnosis were higher under policy B vs policy A. Gain in expected survival since diagnosis according to the IPSS-R model under transplant policy B with respect to a non-transplantation policy were 5.3 years for a patient aged ≤55 years, 4.7 years for a patient aged 60 years and of 2.8 years for a patient aged 65 years. (Figure 3)

Expected survival times were up to three years greater under policy B with respect to policy A for younger patients. When the waiting time before transplantation was progressively increased from 0 to 5 years, there was an increase in expected survival under policy A (in younger patients this increases by about two further years if transplant is delayed until 5 years in low IPSS-R risk state). Conversely, under policy B, delaying transplant further reduces expected survival, by up to about three years with a delay of 5 years after entering intermediate risk state or further progression to high risk state. (Figure 3)

Delaying transplantation after progression to high IPSS-R resulted in lower values for life expectancy compared to those estimated according to policy B, irrespective of the delay time *t*. (*not shown*)

According to these findings, delayed transplantation strategy is advisable for patients with early disease, i.e. very low and low IPSS-R risk, whereas no further delay is advised for patients belonging to intermediate or higher risk categories.

We also calculated the life expectancy based on quality-adjusted life years (QALY). With respect to the natural course of the disease, we assigned QALY51 to the very low IPSS-R risk; QALY50.95 to low and intermediate IPSS-R; and QALY50.90 to high and very high IPSS-R. Evolution to AML was assigned QALY50.85. In patients receiving transplantation, the onset of chronic graft versus host disease, observed in about 30% of cases, lowers the QoL to 0.85: therefore, we set up an average QALY value of 0.9 for post-allogeneic HSCT survival. Adjustment for QoL did not affect the preferred treatment strategy for any of the IPSS-R risk groups (*not shown*).

In order to evaluate the extent to which making a decision based on IPSS rather than IPSS-R may lead to a different transplantation strategy in early disease stage, we cross-tabulated the distribution of patients in the Pavia cohort according to their IPSS and IPSS-R scores. Among patients who at any point during follow-up were classified as low-intermediate1 risk IPSS and therefore candidate to a delayed transplantation according to an IPSS-based strategy,15 29% had an intermediate or higher IPSS-R score at the same time, and as a consequence would benefit from an immediate transplantation according to a IPSS-R based strategy. Overall, there was a 2-year gain in life expectancy using the IPSSR-based policy, and this gain was maximized in younger patients (gain of life expectancy under IPSSR-

based policy vs. IPSS-based policy was 2.62, 1.5 and 0.6 years for patients aged ≤55, 60 and 65 years, respectively)

Effect of hypomethylating agents before transplantation

We then aimed to include the effect of HMAs given as pre-transplant treatment to reduce disease burden in advanced MDS stages.

The effect of treatment with HMAs was obtained from an analysis of the results of two studies, including 278 patients treated with azacitidine. The first study19 presented a hazard ratio (for overall survival, between HMAs and conventional care) of HR = 0.58 (0.43, 0.77). This is converted to a ratio of expected survival times, 1/HR = 1.72 (1.30, 2.33), which assumes an exponential survival distribution 1. The second study 26 presented median overall survival times of 20 (16,26) months in HMAs and 14 (12, 14) in conventional care. The ratio of medians is assumed to be the same as the ratio of means, and a CI for the ratio 1.43 (1.10, 1.86) is obtained by simulation. The pooled estimate, using fixed-effects meta-analysis on the log scale, is 1.55 (1.27, 1.89). To estimate expected survival in the periods when HMAs are given, the equivalent HMA-free survival times (estimated from the cohort data) are multiplied by the ratio of expected survival times.

The following policies are evaluated.

C. Delay transplant until progression to state 3 (intermediate IPSS-R), and then an optional further delay between 0 and 5 years spent in state 3, versus the same but with HMAs treatment beginning on entry to state 3 and ending if transplant is given.

D. Delay transplant until progression to state 4 (high IPSS-R), and then an optional further delay between 0 and 5 years spent in state 4, versus the same but with HMAs treatment beginning on entry to state and ending if transplant is given.

HMA treatment is associated with up to about 2 years longer survival with respect to allo-SCT alone. Intervention in state 3 (IPSS-R intermediate risk) is associated with longer survival than intervention in state 4-5 (IPSS-R high and very high risk). (Figure 4)

Gain in expected survival since diagnosis under policy C (intervention in state 3 – intermediate IPSS-R) performing HMAs before transplantation vs. allo-SCT alone were 1.3 years for a patient aged ≤55 years, 1.6 years for a patient aged 60 years and of 2.4 years for a patient aged 65 years (Figure 4).

Discussion

Patients with MDS may be diagnosed at any stage of the disease, and their life expectancy may vary from several years to few months according to the disease-related risk, which can be assessed using prognostic scores.1,4–6,14,27

Although transplantation early after diagnosis of MDS is associated with the most favourable post-transplantation outcome, it remains unclear whether early transplantation leads to maximal life expectancy for patients with early stage MDS that may experience a

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long period of stable disease after diagnosis.8–11 A previous decision analysis by the IBMTR based on a discrete-time Markov model and concluded that life expectancy of patients with low or intermediate-1 IPSS risk was higher when transplantation was delayed but performed before the progression of AML. Conversely, for high-risk MDS transplantation soon after diagnosis conferred the best prognosis.15 This analysis, however, had some weakness mainly lying in the nature of the data. In fact, clinical features of the non-transplantation cohort were available only at diagnosis and at the time of leukemic progression or death.26 Therefore, this model did not account for disease progression to higher risk categories, which is typical of the natural course of the disease and may significantly affect clinical outcome.14 Nonetheless, a not negligible heterogeneity was observed in IPSS low and intermediate-1 subgroups, and the original score does not include relevant prognostic factors i.e., severe anemia and recently refined cytogenetic risk.6,7 Finally, only patients receiving myeloablative conditioning who were 60 years old or younger were considered. In last years the use of RIC was significantly increased and currently allo-SCT is offered as a therapeutic option in eligible patients until the age of 65-70.

The present study included a cohort of untreated MDS patients with longitudinal clinical data. On this basis, we adopted a continuous-time Markov approach to model the natural course of MDS.27 Data on transplanted patients from the GITMO registry were then used to estimate the effect of transplantation on survival. In addition we adopted IPSS-R, which was shown to improve the prognostic stratification of low-grade MDS and significantly stratify the outcome of transplantation.6–8

Using IPSS-R, the estimated life expectancy was maximized when transplantation was delayed until progression from the very low or low risk to the intermediate risk, and then decreased. Within the low and intermediate-1 IPSS risk, IPSS-R identifies a subgroup of patients (29%) who may benefit from early transplantation. Overall, there was a 2-year gain in life expectancy using the IPSSR-based policy, and this gain was maximized in younger patients.

The availability of HMAs, including azacitidine and decitabine, has changed the landscape of treatment of advanced-stage MDS. Azacitidine results in hematologic improvements in approximately 25-50% of cases and complete response in 10-20% with improved survival compared to supportive care alone in high-risk MDS and with a good toxicity profile compared with induction chemotherapy.19,26 Although HMAs can induce hematological and cytogenetic responses, these therapies do not appear to eradicate MDS clones, 19,20,26 and recent data suggest that even in patients aged 60 to 70 years with advanced disease, transplantation offers overall and quality-adjusted survival benefit with respect to non-transplant procedures (including HMAs). 32

The use of HMAs is increasing as a bridge to more definitive therapy, as a part of a comprehensive strategy to prevent relapse after allo-HSCT in high risk patients. Several studies have evaluated the role of HMAs given before transplantation, though very few were conducted prospectively. Overall, these investigations showed similar posttransplantation outcome for patients receiving HMAs vs. remission-induction chemotherapy, without

significant treatment-related toxicity.21,33 Moreover, in some cases an improved outcome of patients transplanted in complete remission compared to those with active disease at the time of allo-SCT was reported. 21,33.

Our decision analysis seems to suggest that HMAs given before transplantation in advanced MDS stages is associated with a gain of life expectancy, specially in older patients (most of which received RIC and therefore are at higher risk of disease relapse).

In the absence of data from prospective trials on patients with MDS who are candidates for allo-SCT, at present, the decision to perform a cytoreductive treatment should be made on an individual basis, accounting for clinical considerations with respect to each specific patient. 16–18 As the rate of complete remissions is generally higher with induction chemotherapy compared to HMAs, that strategy might still be the best option in selected medically fit patients e.g. in the context of innovative transplant protocols and the immediate availability of a suitable donor. On the other hand, HMAs could be considered mainly for older patients (including those with extra-hematological comorbidity) which are at risk of losing eligibility for a transplantation procedure as a result of death or treatment-related toxicity and as a bridging strategy to allo-SCT in those where no donor has yet been identified.4,18,21

There are potential limitations in our analysis. First, our model did not into account for some patient-related factors which may affect post-transplantation outcome, such as comorbidity. In addition, methodological limitations of Markov models are to be considered. One point is the potential bias in the effect of transplantation from failing to account for early treatment-related mortality. By modelling a time-dependent effect of allo-SCT, our multi-state model can separate early treatment-related mortality from later survival benefits from treatment. However, these effects are estimated from observational data, which assume that selection of patients for transplant is related only to predictors of survival that are modelled, in our case, the IPSS-R risk score.34

In summary, the findings of our study indicate that a delayed transplantation strategy is advisable for patients with early disease, that is, those with very low or low IPSS-R risk. Allogeneic HSCT should instead be immediately offered to eligible patients belonging to intermediate risk category, since this strategy offers the best survival benefit. In advanced disease stages, preliminary evidence suggest that HMAs administered before transplant, may have a positive impact on life expectancy. In the absence of prospective randomized data, these results provide clinicians with a base of evidence to maximize the effectiveness of allo-SCT in MDS patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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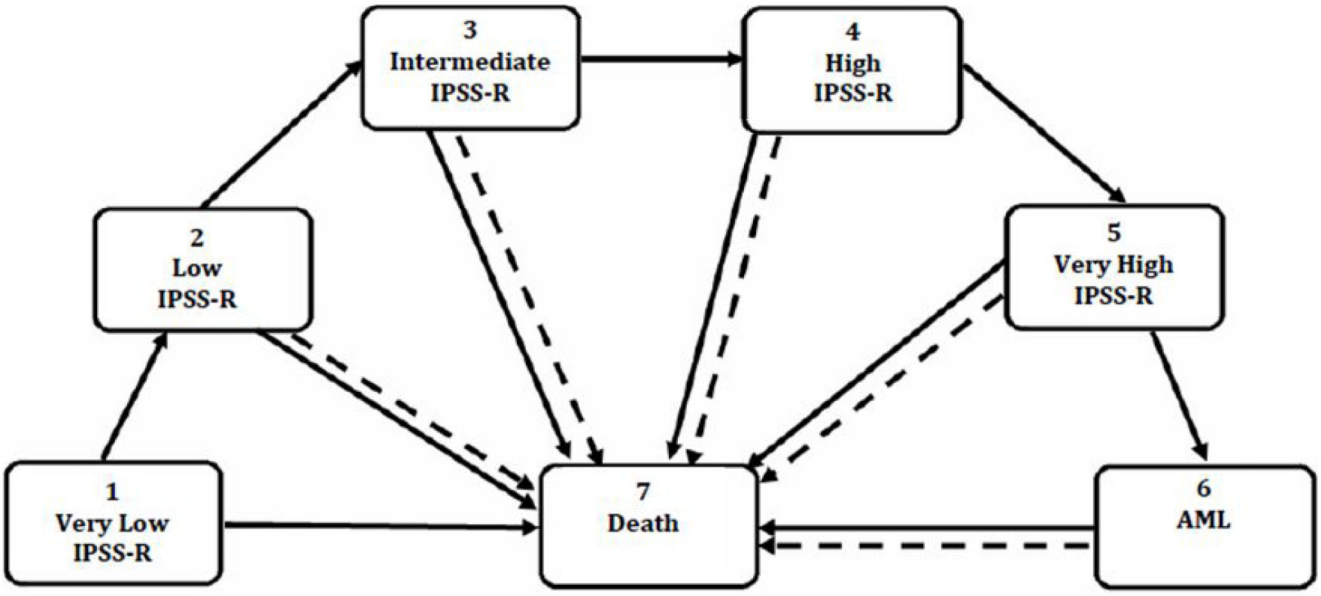

Figure 1.

Markov continuous-time Multi-State Models of the MDS natural history. IPSS-R risk scores were adopted as time-dependent indicators of the natural course of MDS. Allo-SCT was modelled as a time-dependent covariate, and its effect on survival was estimated as a hazard ratio with respect to the “no allo-SCT” category. Solid arrows represent transitions according to the natural course of the disease, whereas the effect of allo-SCT on mortality (i.e. transition to death) in each state is represented by dot arrows.

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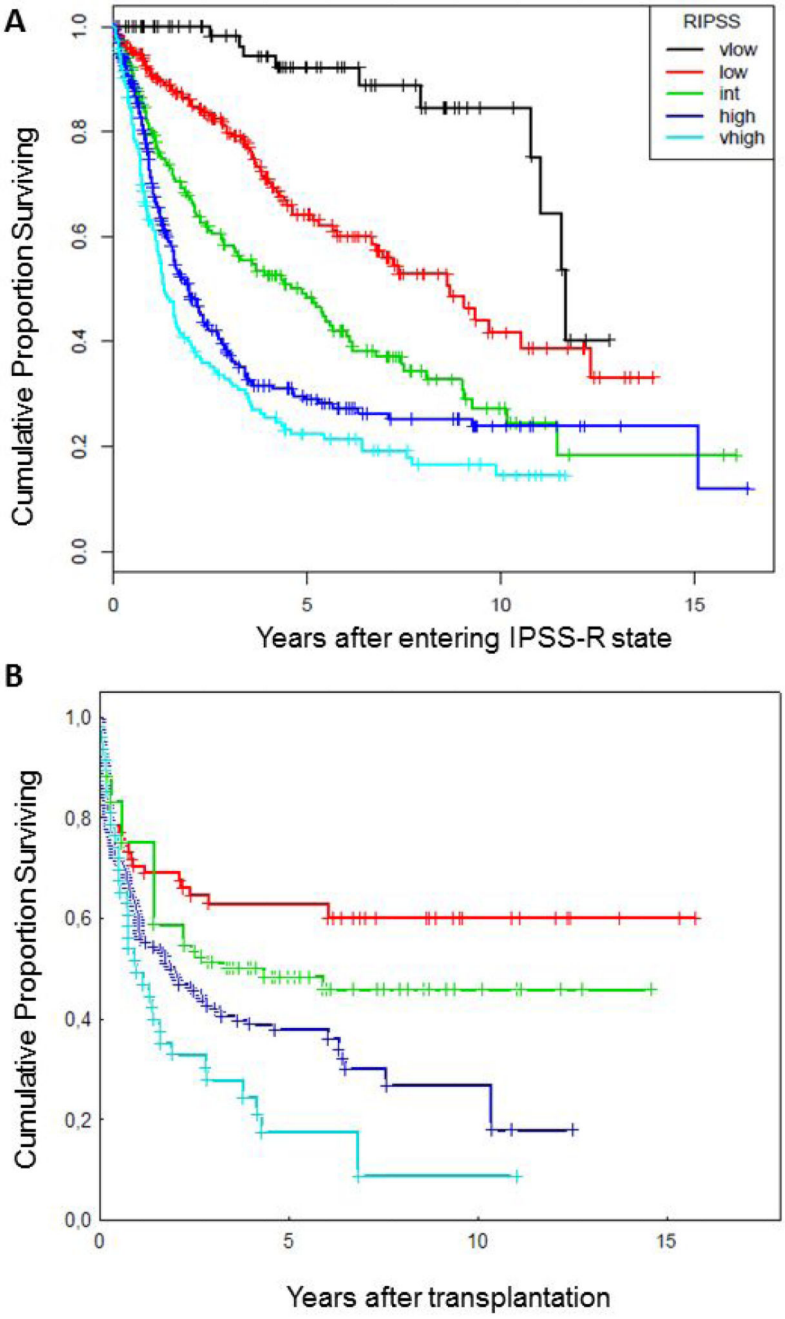

Figure 2.

Overall survival of MDS patients. A: overall survival in the Pavia cohort classified by time-dependent IPSS-R; B: overall survival in the GITMO cohort classified into IPSS-R groups evaluated at the time of allo-SCT.

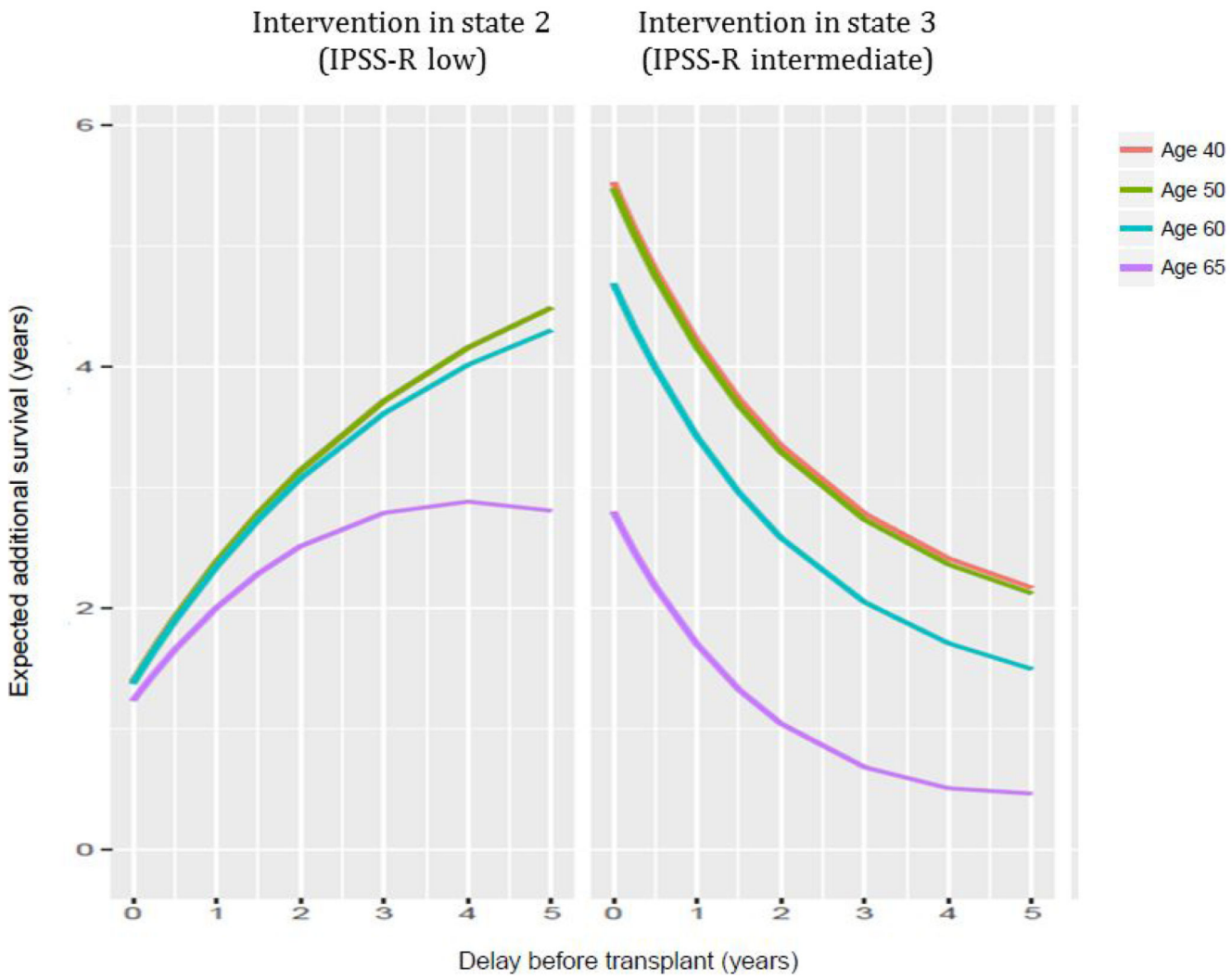

Figure 3.

Gain in expected survival under different transplant policies with respect to a nontransplantation policy. We assumed that the MDS patient was classified as very low IPSS-R risk at the time of diagnosis. Each policy was then evaluated for a set of different ages at diagnosis (as shown in the box) and for different waiting times t (between 0 and 5 years since entering any disease state).

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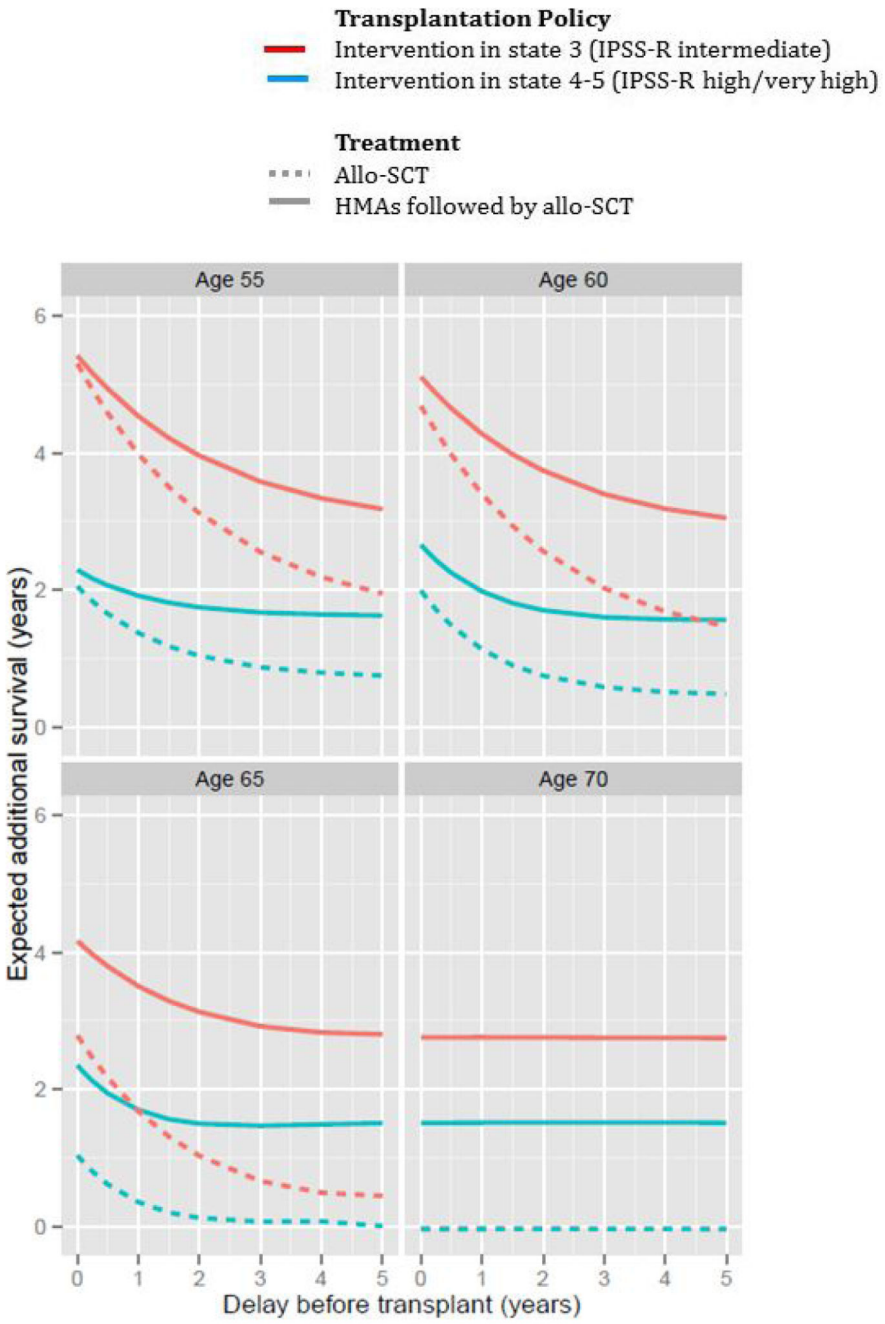

Figure 4.

Expected additional survival (compared to no-intervention), by transplant policy, age and treatment with HMA.

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Table 1

Clinical characteristics of patients classified according to WHO criteria. A) patients of the Pavia cohort, that included subjects who mainly received supportive care and were regularly followed-up. B-C) patients of the GITMO transplantation cohort classified according to WHO criteria (B, clinical characteristics and C, transplantation-related features).D) patients treated with hypomethylating agents (HMA, meta-analysis of two randomized studies)

A) Pavia cohort	
Characteristics at diagnosis	
Number of patients	961
Median age (range)	66 (19-81)
Sex (male/female)	557(58%)/404(42%)
WHO classification: *	
RCUD	173 (18%)
RARS	96 (10%)
MDS del (5q)	48 (5%)
RCMD	356 (37%)
RAEB-1	153 (16%)
RAEB-2	134 (14%)
Hb (g/dl)	9.3 (6.4-13.5)
Absolute Neutrophil Count (x10^9 L)	1.430 (0.10-3.290)
PLT (x10^9 L)	105 (5-732)
Cytogenetics **	874/961 (91%)
Very low risk	26 (3%)
Low risk	603 (69%)
Intermediate risk	149 (17%)
Poor risk	61 (7%)
Very poor risk	35 (4%)
Transfusion-dependency ***	317 (33%)
IPSS-R risk	874/961 (91%)
Very-low	157 (18%)
Low	244 (28%)
Intermediate	184 (21%)
High	219 (25%)
Very high	70 (8%)
Treatment	
Supportive care	711 (74%)
Erythropoietin	173 (18%)
Lenalidomide	11 (1%)
Low-dose chemotherapy	19 (2%)
Hypomethylating agents	106 (11%)
AML-like chemotherapy	38 (4%)

A) Pavia cohort	
Characteristics at diagnosis	
Allo-SCT	67 (7%)

B) GITMO Transplantation cohort		
Characteristics at transplantation*	**MDS**	**AML-MDS****
Number of patients	344	145
Median age	48 (19-68)	47 (21-70)
Sex (Male/Female)	179 (52%)/165(48%)	74(51%)/71(49%)
WHO classification:		
RCUD/RARS/MDS del(5q)	31 (9%)	-
RCMD	76 (22%)	
RAEB-1	86 (25%)	
RAEB-2	151 (44%)	
Hb (g/dl)	9.2 (6.9-12.8)	8.7 (6.4-11)
Absolute Neutrophil Count (x10^9 L)	1.12 (0.01-8.3)	1.18 (0.2-2.4)
PLT (x10^9 L)	53 (3-491)	48 (7-231)
Cytogenetics: ***	320/344(93%)	117/145 (81%)
Very Good	3 (1%)	-
Good	163 (51%)	51 (44%)
Intermediate	84 (26%)	32 (27%)
Poor	38 (12%)	19 (16%)
Very Poor	32 (10%)	15 (13%)
Transfusion-dependency ****	230/344 (67%)	110/145 (76%)
IPSS-R risk	320/344(93%)	117/145 (81%)
Very-low	-	
Low	38 (12%)	
Intermediate	77 (24%)	8 (7%)
High	166 (38%)	56 (48%)
Very high	39 (26%)	53 (45%)

c) Transplant-related features of 489 patients classified according to WHO criteria		
	MDS	**AML-MDS**
Number of patients	344	145
Time from diagnosis to allo-SCT (months)	10 (1-313)	8 (1-352)
Type of donor: *		
Sibling	224 (65%)	91 (63%)
Unrelated donor	120 (35%)	54 (37%)
Source of Hematopoietic Stem Cells:		
Peripheral blood / Cord blood	217 (63%)	81 (56%)
Bone marrow	127 (37%)	64 (44%)

c) Transplant-related features of 489 patients classified according to WHO criteria		
	MDS	**AML-MDS**
Untreated:	251/344 (73%)	13/145 (9%)
Remission-induction treatment: **	93/344 (27%)	129/145 (89%)
Complete remission	47/93 (51%)	57/129 (44%)
- AML-like chemotherapy	67/93 (72%)	120/129 (93%)
Complete remission	38/67 (57%)	54/120 (45%)
- HMAs	26/93 (28%)	9/129 (7%)
Complete remission	9/26 (35%)	3/9 (33%)
Conditioning regimen ***		
Standard conditioning regimen	220 (64%)	91 (63%)
Reduced-intensity conditioning (RIC)	124 (36%)	54 (37%)

D) HMA cohort		
Clinical features#	**Silverman et al (2002)***	**Fenaux et al (2009)****
Number of patients	99	179
Median age	69 (31-92)	69 (42–83)
Sex (Male/Female)	72(73%)/27(27%)	132 (74%)/47 (26%)
WHO classification:		
RCUD/RARS/MDS del(5q)	22 (22%)	-
RCMD		-
RAEB-1	32 (32%)	14 (8%)
RAEB-2		98 (55%)
MDS/AML	27 (27%)	55 (31%)
Other	18 (18%)	12 (7%)
Cytogenetics: ***		170/179 (95%)
Good		83 (49%)
Intermediate		37 (22%)
Poor		50 (29%)
IPSS risk		163/179 (91%)
Low	2 (2%)	-
Intermediate-1	21 (26%)	5 (3%)
Intermediate-2	9 (11%)	76 (47%)
High	7 (9%)	82 (50%)
Azacitidine, cicles (n)		9 (4-15)
Complete remission	7 (7%)	30 (17%)
Partial remission	16 (16%)	21 (12%)
Stable disease	37 (37%)	75 (42%)

* RCUD: refractory cytopenia with unilineage dysplasia; RARS: refractory anemia with ringed sideroblasts; MDS del(5q): myelodysplastic syndrome with del(5q); RCMD: refractory cytopenia with multilineage dysplasia; RAEB: refractory anemia with excess blasts.

** cytogeneitc risk was stratified according to IPSS-R criteria

*** transfusion dependency was defined according to WPSS criteria

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* all clinical variables were analyzed at the time of transplantation in patients undergoing upfront allogeneic-SCT and at the time of remission-induction chemotherapy in those receiving treatment before transplantation

** including patients affected with AREB in transformation according to FAB classification

*** cytogeneitc risk was stratified according to IPSS-R criteria

**** transfusion dependency was defined according to WPSS criteria

* Criteria for selection of HLA-matched unrelated donors before 2002 included low-resolution typing for HLA class I (A,B) and high-resolution typing for HLA-DRB1, whereas since 2002 criteria included high-resolution typing for both HLA class I (A,B,C) and class II alleles (DRB1/3/4/5, DQA1, DPB1).). According to GITMO policy, in the absence of an 8/8 HLA-matched donor, one allele mismatched (class I or II) donor was allowed. Overall 174 patients received an allo-SCT form unrelated donor (138 [79%] from matched and 36 [21%] from mismatched donor)

** response to treatment was defined according to IWG 2006 criteria

** Most frequent conditioning regimens included the following: total body irradiation (TBI) and cyclophosphamide (20% of cases), TBI and fludarabine (8%), busulphan and cyclophosphamide (30%), thiotepa and cyclophosphamide (24%), and thiotepa and fludarabine (11%). For most patients, graft-versus-host disease (GVHD) prophylaxis was combined cyclosporine and methotrexate. The conditioning regimens were defined as standard myeloablative or at reduced intensity according to internationally recognized definition (Bacigalupo et al Biol Blood Marrow Transplant. 2009 Dec; 15(12): 1628–1633.) In patients aged ≤55 years, standard conditioning was administered in 76% of cases, while 24% of subjects received RIC; in patients aged > 55 years, a RIC was used in 72% of cases, while 28% of subjects received standard conditioning.

clinical variables were analysed before treatment with azacitidine

* J Clin Oncol. 2002 May 15;20(10):2429-40 and

** Lancet Oncol. 2009 Mar;10(3):223-32. Exclusion criteria for both clinical trials were: poor performance status and baseline organ dysfunction (total bilirubin > 1.5 ULN, AST/ALT > 2 ULN, Serum creatinine > 1.5 ULN).

*** cytogeneitc risk was stratified according to IPSS criteria

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Table 2

Expected survival (95% confidence intervals) in years by transplant policy A and B, age at diagnosis and time in months t of transplant decision

		Age at diagnosis								
Policy A	**Delay time t**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**
IPSS-R low	0	16.39 (11.21,24.33)	16.37 (11.21,24.24)	16.35 (11.21,24.13)	16.32 (11.22,23.9)	16.23 (11.24,23.52)	16.08 (11.29,22.84)	15.75 (11.38,21.62)	15.17 (11.56,19.46)	13.97 (11.04,16.89)
	1	16.49 (11.45,24.15)	16.48 (11.45,24.09)	16.45 (11.45,23.96)	16.41 (11.47,23.76)	16.32 (11.48,23.4)	16.16 (11.52,22.7)	15.82 (11.58,21.47)	15.2 (11.69,19.34)	13.97 (11.04,16.89)
	3	16.68 (11.82,23.88)	16.66 (11.83,23.83)	16.64 (11.83,23.72)	16.6 (11.83,23.49)	16.5 (11.85,23.14)	16.32 (11.86,22.47)	15.95 (11.89,21.25)	15.27 (11.88,19.13)	13.97 (11.04,16.89)
	6	16.94 (12.3,23.42)	16.92 (12.3,23.38)	16.89 (12.31,23.29)	16.84 (12.32,23.07)	16.73 (12.32,22.73)	16.53 (12.3,22.09)	16.13 (12.26,20.93)	15.35 (12.09,18.93)	13.97 (11.04,16.89)
	12	17.37 (12.96,22.96)	17.35 (12.96,22.89)	17.32 (12.96,22.79)	17.25 (12.95,22.57)	17.13 (12.95,22.25)	16.89 (12.92,21.67)	16.42 (12.77,20.56)	15.48 (12.37,18.65)	13.97 (11.04,16.89)
	18	17.71 (13.38,22.98)	17.69 (13.38,22.87)	17.65 (13.38,22.75)	17.58 (13.36,22.58)	17.44 (13.34,22.23)	17.17 (13.27,21.62)	16.63 (13.06,20.5)	15.57 (12.57,18.57)	13.97 (11.04,16.89)
	24	17.99 (13.59,23.09)	17.96 (13.58,23.04)	17.92 (13.58,22.9)	17.84 (13.56,22.68)	17.69 (13.52,22.32)	17.39 (13.42,21.67)	16.79 (13.17,20.48)	15.62 (12.6,18.54)	13.97 (11.04,16.89)
	36	18.37 (13.77,23.5)	18.34 (13.77,23.42)	18.3 (13.76,23.32)	18.21 (13.75,23.09)	18.03 (13.69,22.71)	17.69 (13.58,21.97)	17 (13.26,20.69)	15.66 (12.63,18.55)	13.97 (11.04,16.89)
	48	18.61 (13.84,23.89)	18.58 (13.83,23.383)	18.54 (13.82,23.69)	18.44 (13.8,23.45)	18.24 (13.76,23.03)	17.87 (13.62,22.24)	17.12 (13.32,20.87)	15.65 (12.56,18.56)	13.97 (11.04,16.89)
	60	18.76 (13.91,24.23)	18.73 (13.9,24.13)	18.69 (13.89,23.96)	18.58 (13.87,23.68)	18.37 (13.8,23.25)	17.97 (13.67,22.44)	17.18 (13.36,20.97)	15.62 (12.5,18.54)	13.97 (11.04,16.89)

Policy B	**Delay time t**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**
IPSS-R intermediate	0	19.01 (13.87,24.94)	18.97 (13.86,24.85)	18.9 (13.84,24.69)	18.8 (13.82,24.41)	18.56 (13.77,23.83)	18.1 (13.65,22.85)	17.2 (13.29,21.15)	15.62 (12.5,18.53)	13.96 (11.05,16.9)
	1	18.9 (13.85,24.66)	18.86 (13.85,24.56)	18.79 (13.82,24.41)	18.69 (13.81,24.14)	18.45 (13.76,23.6)	18 (13.63,22.64)	17.11 (13.3,20.96)	15.55 (12.47,18.45)	13.96 (11.05,16.9)
	3	18.69 (13.83, 24.15)	18.65 (13.83,24.09)	18.59 (13.83,23.92)	18.48 (13.81,23.63)	18.25 (13.75,23.11)	17.8 (13.6,22.21)	16.93 (13.24,20.57)	15.42 (12.4,18.26)	13.96 (11.05,16.9)
	6	18.4 (13.79,23.46)	18.36 (13.79,23.37)	18.3 (13.78,23.25)	18.2 (13.75,22.95)	17.97 (13.69,22.47)	17.53 (13.54,21.61)	16.69 (13.17,20.11)	15.24 (12.31,18.02)	13.96 (11.05,16.9)
	12	17.9 (13.72,22.25)	17.87 (13.72,22.17)	17.8 (13.7,22.06)	17.72 (13.67,21.85)	17.5 (13.6,21.44)	17.09 (13.42,20.71)	16.29 (12.99,19.42)	14.96 (12.1,17.71)	13.96 (11.05,16.9)
	18	17.49 (13.55,21.53)	17.46 (13.55,21.47)	17.41 (13.54,21.34)	17.32 (13.52,21.13)	17.12 (13.45,20.71)	16.73 (13.29,20.04)	15.98 (12.87,18.88)	14.74 (11.94,17.51)	13.96 (11.05,16.9)
	24	17.17 (13.47,20.89)	17.14 (13.46,20.8)	17.09 (13.45,20.68)	17 (13.41,20.47)	16.81 (13.34,20.11)	16.44 (13.16,19.5)	15.73 (12.7,18.55)	14.59 (11.81,17.37)	13.96 (11.05,16.9)
	36	16.69 (13.19,20.01)	16.66 (13.18,19.93)	16.62 (13.17,19.84)	16.54 (13.14,19.66)	16.36 (13.06,19.39)	16.02 (12.89,18.9)	15.38 (12.44,18.12)	14.39 (11.55,17.2)	13.96 (11.05,16.9)
	48	16.38 (13,19.56)	16.35 (13,19.49)	16.31 (12.98,19.41)	16.23 (12.94,19.27)	16.07 (12.88,19.01)	15.75 (12.69,18.59)	15.16 (12.26,17.93)	14.29 (11.44,17.14)	13.96 (11.05,16.9)
	60	16.17 (12.81,19.3)	16.15 (12.81,19.24)	16.1 (12.8,19.15)	16.03 (12.78,19.02)	15.88 (12.7,18.78)	15.58 (12.54,18.39)	15.02 (12.16,17.79)	14.27 (11.4,17.12)	13.96 (11.05,16.9)