Impact of red blood cell transfusion dose density on progression-free survival in patients with lower-risk myelodysplastic syndromes

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Supplementary Material

Supplementary Method Section

Data Handling and Exclusions

The dataset contained data from 1504 patients having three or more visits recorded. Within this dataset, there were 368 deaths and 181 progressions to high-risk MDS or AML, which were considered as events for this analysis. The following exclusions were made:

- 2 patients with RAEB-2 were removed leaving 1502 patients.
- 1 patient was deleted as the subject had a very long pre-diagnosis transfusion history.

These exclusions leave 1501 patients in the cohort.

We also removed all patients that had completely missing values for any of the following variables: Haemoglobin (0 patients have all observations missing), neutrophils (2 patients), platelets (1 patient), bone marrow blast count (60 patients), cytogenetic risk category (112 patients), EQ5D-index (101 patients).

This left a total of 1267 patients in the analysis dataset, with 407 deaths of which 90 had progression. 72 Patients survived until the end of the study period but progressed to high-risk MDS or AML.

For the analysis dataset, missing values in these variables were imputed with last observation carried forward or next observation carried back.

Handling of missing transfusion data

10 remaining subjects were flagged as having received transfusions before diagnosis, but were missing the number of units received. Those 4 transfused more than a year before diagnosis were set to no transfusions received. Those 6 transfused less than a year before diagnosis were assigned either an imputed 2 units (a plausible figure) or 4 units (the mean number received among those receiving pre-diagnosis transfusion) according to the actual length of time before diagnosis.

Six additional subjects were identified as having received transfusions a very long time before diagnosis (more than 600 days). These patients were set to not having received pre-diagnosis transfusions unless they had received more than 7 units (3 patients).

The Definition of Dose Density

For each patient, the transfusion data available consisted of the number of units received between each visit. This variable, which we call dose, is expressed as an average of "units received per month" in each inter-visit interval.

The analysis used is proportional hazards regression with time-varying covariates. The basic interval on which all variables are defined is the interval between visits. Therefore, covariates are assigned to be piecewise constant on these time intervals.

In standard survival analysis, the hazard at any instant is assumed to be modified by the value of the explanatory variables at that instant. This presented three problems for the analysis with the dose transfusion variable:

- For many patients in this dataset, the value of the recorded transfusion dose variable is very "spiky", varying strongly over time. It seems unlikely that the actual value of the hazard would follow such a form.
- It is unlikely that the hazard will respond instantaneously to the transfusion dose received.
- It is observed that, in this dataset, patients receive fewer transfusions in the interval in which death occurs, than in the intervals before the interval in which death occurs (Supplement figure 1). Presumably, the treatment focus switches to palliative care on the approach to death. This would mean that the event of death is correlated with zero or low values of transfusion dose, leading to a hazard estimate that is high for low values of dose and which reduces as dose increases.

Rather, it seems more likely that the association between transfusions and hazard would be better expressed as an association with some sort of cumulative dose value (reflecting the idea that the hazard at any time is proportional to the total dose received) or with some other "smoothed" variable that reflects an average rate of receiving transfusions.

In order to perform this smoothing, the cumulative total dose at the end of each inter-visit time interval was calculated. This was then divided by the time (in months) since the beginning of the time interval in which the first post-diagnosis transfusion was received, giving a dose-density measurement. This dose-density is then assigned to each time interval. The value of this variable at each point in time represents the average rate at which the patient has been receiving units of blood

since they started transfusions. This main variable of interest, the dose density, was modelled in regression analysis using restricted cubic splines with four knots.

With the dose density defined as such, the hazard is taken as proportional to the number of units received since transfusions started divided by the time since transfusions started. The effect of this is to allow the hazard to depend upon something that has happened in the past; but the strength of the effect will decay as time passes and no further transfusions are received. Contrast this with simply using the cumulative number of units received at any point in time. Here, again, the effect on the hazard is proportional to the dose received in the past, but there is now no decay in the size of the effect.

Results

Supplementary Table 1: Baseline Characteristics from time of diagnosis & PFS, stratified according to transfusion status at landmark (Visit 3)

	Total	Hazard Ratio (95%CI)	Adjusted Hazard Ratio[1] (95%CI) (95%CI)	Transfusion Status at landmark	
				No	yes
Total	1267 (100.0)			751 (100.0)	516 (100.0)
Country:					
Austria	86 (6.8)	0.84 (0.56 - 1.27)	0.76 (0.49 - 1.18)	61 (8.1)	25 (4.8)
Czech Republic	94 (7.4)	0.82 (0.57 - 1.19)	0.89 (0.61 - 1.31)	43 (5.7)	51 (9.9)
Denmark	47 (3.7)	1.94 (1.25 - 3.02)	1.97 (1.26 - 3.07)	17 (2.3)	30 (5.8)
France	313 (24.7)	1	1	200 (26.6)	113 (21.9)
Germany	25 (2.0)	1.09 (0.62 - 1.94)	1.34 (0.75 - 2.40)	17 (2.3)	8 (1.6)
Greece	128 (10.1)	0.85 (0.60 - 1.20)	0.90 (0.63 - 1.30)	81 (10.8)	47 (9.1)
Israel	67 (5.3)	0.83 (0.46 - 1.47)	0.92 (0.51 - 1.64)	47 (6.3)	20 (3.9)
Italy	46 (3.6)	0.47 (0.23 - 0.96)	0.62 (0.30 - 1.27)	33 (4.4)	13 (2.5)
Netherlands	44 (3.5)	0.75 (0.44 - 1.29)	0.96 (0.56 - 1.65)	28 (3.7)	16 (3.1)
Poland	31 (2.4)	1.96 (1.19 - 3.22)	1.45 (0.85 - 2.47)	13 (1.7)	18 (3.5)
Portugal	2 (0.2)	-	-	0 (0.0)	2 (0.4)
Romania	17 (1.3)	0.28 (0.09 - 0.87)	0.15 (0.05 - 0.50)	7 (0.9)	10 (1.9)
Serbia	14 (1.1)	2.02 (0.94 - 4.33)	1.32 (0.61 - 2.87)	5 (0.7)	9 (1.7)
Spain	85 (6.7)	1.01 (0.67 - 1.53)	1.18 (0.77 - 1.79)	54 (7.2)	31 (6.0)
Sweden	88 (6.9)	0.87 (0.61 - 1.24)	0.99 (0.68 - 1.43)	45 (6.0)	43 (8.3)
United Kingdom	180 (14.2)	0.99 (0.75 - 1.32)	1.07 (0.80 - 1.44)	100 (13.3)	80 (15.5)
Ring Sideroblasts:					
No	967 (76.3)	1	1	581 (77.4)	386 (74.8)
Yes	300 (23.7)	0.83 (0.68 - 1.03)	0.78 (0.63 - 0.98)	170 (22.6)	130 (25.2)
IPSS cytogenetic score					
Good	1052 (83.0)	1	1	655 (87.2)	397 (76.9)
Intermediate	170 (13.4)	1.87 (1.49 - 2.35)	1.92 (1.52 - 2.43)	73 (9.7)	97 (18.8)
Poor	15 (1.2)	2.30 (1.18 - 4.46)	2.36 (1.21 - 4.60)	6 (0.8)	9 (1.7)
Cytogenetics not done	30 (2.4)	0.68 (0.35 - 1.32)	0.68 (0.35 - 1.32)	17 (2.3)	13 (2.5)

	Total	Hazard Ratio (95%CI)	Adjusted Hazard Ratio[1] (95%CI) (95%CI)	Transfusion Status at landmark	
				No	yes
Revised IPSS cytogenetic score					
Very good	121 (9.6)	0.94 (0.66 - 1.33)	0.86 (0.60 - 1.23)	87 (11.6)	34 (6.6)
Good	963 (76.0)	1	1	594 (79.1)	369 (71.5)
Intermediate	141 (11.1)	2.56 (2.02 - 3.25)	2.47 (1.93 - 3.15)	55 (7.3)	86 (16.7)
Poor/ Very Poor	23 (1.8)	1.41 (0.75 - 2.65)	1.26 (0.67 - 2.38)	9 (1.2)	14 (2.7)
Not known	19 (1.5)	1.81 (0.99 - 3.29)	1.63 (0.89 - 3.00)	6 (0.8)	13 (2.5)

Legend: Baseline characteristics of the included patients from time of diagnosis and progression-free survival, stratified according to transfusion status at landmark (Visit 3).

[1]Hazard Ratios (HR) & 95% Confidence Intervals (CI) adjusted for all other variables, as described in Table 1 in the manuscript,

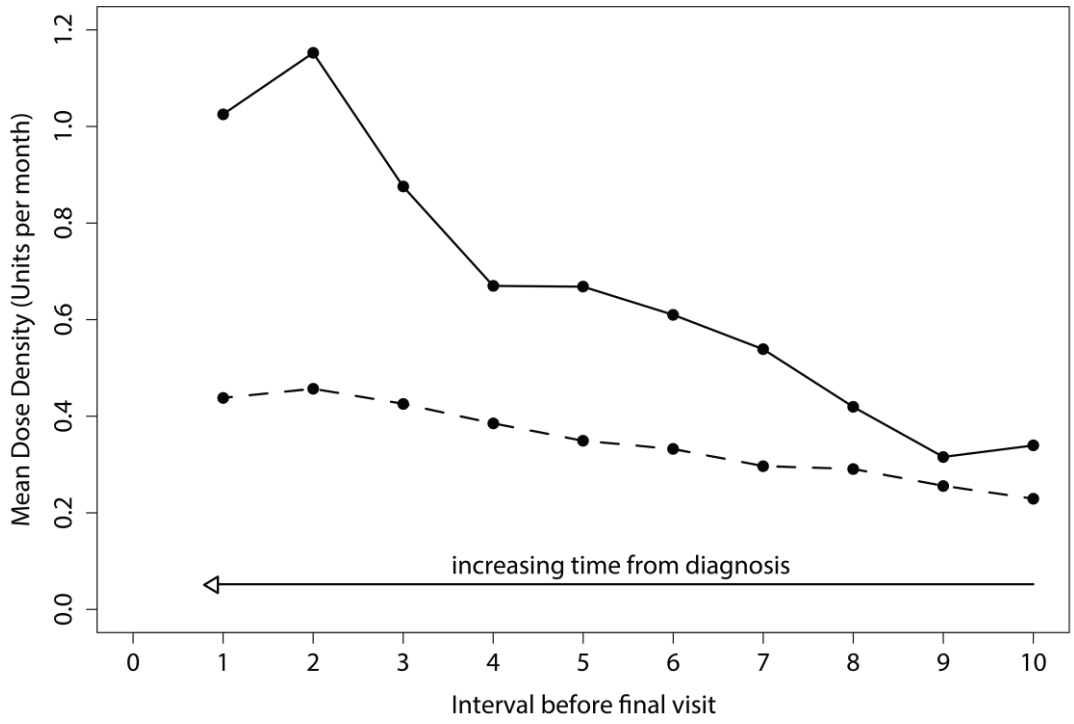
Supplementary Table 2 Characteristics at time of landmark Visit 3 stratified according to transfusion status at landmark (Visit 3)

	Total	Transfusion Status at landmark	
		No	Yes
Total	1267 (100.0)	751 (100.0)	516 (100.0)
Median age at visit 3	74.5 (20.1 - 96.3)	74.2 (20.1 - 92.9)	74.8 (22.2 - 96.3)
WHO Diagnosis[2]:			
RA	130 (10.3)	82 (10.9)	48 (9.3)
RARS	166 (13.1)	91 (12.1)	75 (14.5)
RCMD	328 (25.9)	190 (25.3)	138 (26.7)
RCMD-RS	46 (3.6)	23 (3.1)	23 (4.5)
RAEB-1	103 (8.1)	57 (7.6)	46 (8.9)
RAEB-2	30 (2.4)	5 (0.7)	25 (4.8)
MDS-U	27 (2.1)	21 (2.8)	6 (1.2)
Deletion 5q	70 (5.5)	31 (4.1)	39 (7.6)
Bone Marrow not done	367 (29.0)	251 (33.4)	116 (22.5)
MDS-CI[3]:			
Low	928 (73.2)	583 (77.6)	345 (66.9)
Intermediate	293 (23.1)	154 (20.5)	139 (26.9)
High	35 (2.8)	10 (1.3)	25 (4.8)
Not known	11 (0.9)	4 (0.5)	7 (1.4)
Karnofsky Status:			
80-100	738 (58.2)	496 (66.0)	242 (46.9)
50-70	205 (16.2)	74 (9.9)	131 (25.4)
10-40	25 (2.0)	11 (1.5)	14 (2.7)
Not known	299 (23.6)	170 (22.6)	129 (25.0)
Quality of life			
Visual analogue score, mean (sd)	69.7 (19.0)	73.6 (18.5)	64.1 (18.2)
Revised IPSS category			
Very low	384 (30.3)	305 (40.6)	79 (15.3)
Low	576 (45.5)	314 (41.8)	262 (50.8)
Intermediate	203 (16.0)	88 (11.7)	115 (22.3)
High	45 (3.6)	16 (2.1)	29 (5.6)
Very high	4 (0.3)	1 (0.1)	3 (0.6)
Not known	55 (4.3)	27 (3.6)	28 (5.4)

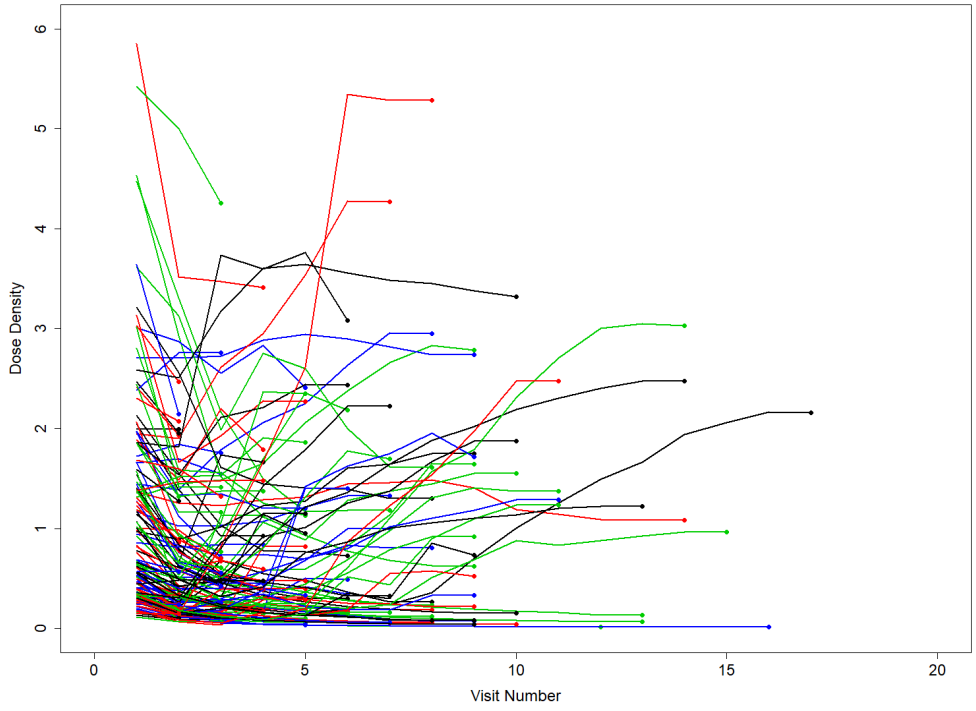
[2]Refractory anemia (RA), Refractory anemia with ring sideroblasts (RARS), Refractory cytopenia with multilineage dysplasia (RCMD), Refractory cytopenia with multilineage dysplasia & ring sideroblasts (RARS), Refractory anemia with excess blasts-1 (RAEB-I), Refractory anemia with excess blasts-2 (RAEB-II), Refractory anemia with excess blasts-2 (RAEB-II), Myelodysplastic syndrome, unclassifiable (MDS-U).

[3]Myelodysplastic syndrome-specific comorbidity index (MDS-CI).

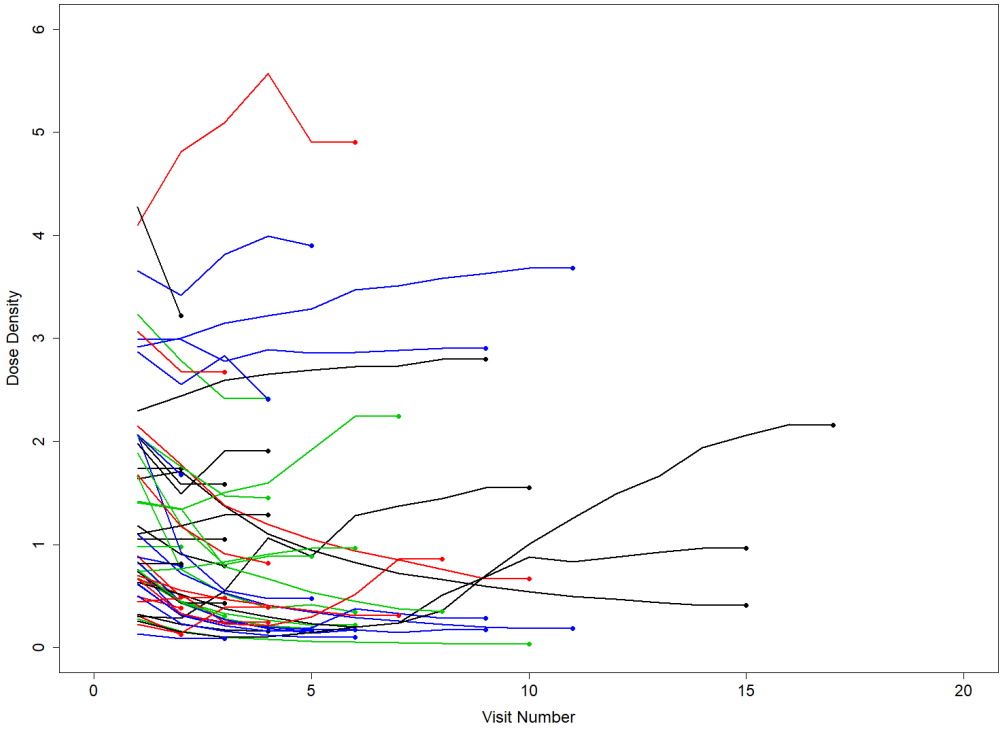
Supplementary figure 1: Mean number of transfused units per month, counting back from the final interval before death, transformation (solid line) or censoring for last interval report, alive and well (broken line).



Supplementary figure 2 Dose Density Trajectories for all Subjects with Initial Response to ESA.



Supplementary figure 3 Dose Density Trajectories for all Subjects with Initial Response to Lenalidomide.



Supplementary figure 4 Dose Density Trajectories for all Subjects with Initial Response to Iron Chelation.