Iron overload and chelation therapy in patients with lower risk myelodysplastic syndromes

Master’s thesis in Medicine

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Abstract

Iron overload and chelation therapy in patients with lower risk myelodysplastic syndromes

Background
Myelodysplastic syndromes (MDS) are malignant disorders characterized by a deficient and disorderly hematopoiesis. The International Prognostic Scoring System divides the patients’ diseases into Low, Intermediate-1, Intermediate-2 and High risk. Low and Intermediate-1 are considered “lower risk” in clinical practice. Red cell transfusions are a common therapy for lower-risk MDS and therefore many patients receive a large number of transfusions during their disease which results in iron overload (IO). This may be treated with iron chelation therapy (ICT), yet the benefits in MDS patients are disputable.

Aims
To identify all MDS patients at Sahlgrenska University Hospital 2009-2014 that met the criteria for ICT and see how many of these patients actually were given ICT as well as look at the impact of ICT regarding transfusion dependency, S-ferritin and overall survival by comparing chelated and non-chelated patients.

Methods
Data was collected from the INCA-registry and electronic hospital journals. Our cohort was defined as lower risk MDS patients diagnosed or treated 2009-2014 at Sahlgrenska with end of 2014 as censoring date. We compared number of transfusions, S-ferritin-levels, overall survival and given therapy as well as other monitoring factors between chelated and non-chelated patients.

Results
Sixty-nine patients were found with lower-risk MDS. Twenty-seven met the criteria for ICT but only nine patients had received ICT. There were no significant differences in transfusion dependency (P=0.883) or S-ferritin (P=0.107) between the groups. Median overall survival
from date of indication was 13 months longer in chelated patients (P=0.045), (23 vs 10 months, chelated and non-chelated patients).

**Conclusions**
Our results may indicate that chelation therapy could improve survival in heavily transfused lower risk MDS patients as suggested in several retrospective studies, but prospective studies are warranted.

**Key words:**
Myelodysplastic syndromes, iron overload, iron chelation therapy
Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of malignant disorders of the hematopoietic stem cells in the bone marrow. They are characterized by a deficient and disorderly hematopoiesis resulting in various degrees of cytopenias and a risk of developing acute myeloid leukemia (AML). The variations in symptoms and prognosis are vast. Whereas some patients present with profound pancytopenia and rapid progress to AML others may live for many years with asymptomatic anemia \(^1, 2\). The median age at diagnosis is 75 years, male to female ratio is 60:40 \(^3\). Diagnosis is based on whole blood count, bone marrow morphology and chromosome karyotyping. The WHO 2008 Classification \(^4\) divides the myelodysplastic disorders based on these factors as shown in the table below (Table 1).

In addition to the WHO classification there is a scoring system known as the International Prognostic Scoring System (IPSS) using the number of cytopenias (hemoglobin <100 g/L, ANC <1.8 x10^9/L, platelets <100 x10^9/L), the number of blasts seen in the bone marrow as well as karyotype to estimate the risk score \(^5\). This estimates the prognosis of a specific patient (see Table 2). With the IPSS score the conditions are divided into Low, Intermediate-1 (INT-1), Intermediate-2 (INT-2) and High risk MDS. In clinical practice the terms “lower risk” meaning IPSS Low risk and INT-1, and “higher risk” meaning IPSS INT-2 and High risk are used.

The Revised International Prognostic Scoring System (IPSS-R) was introduced in 2012 \(^6\). This was an update of the previous IPSS system where several different clinical features in such as patient age, number of blasts down to two percent and a more thorough separation of the cytogenetic differences were added to the classification. We have chosen to use the IPSS system since The R-IPSS were introduced in 2012, and our cohort is from 2009-14.

The primary therapy for lower risk MDS patients is erythropoiesis-stimulating agents (ESA)
and/or Granulocyte colony stimulating factor (G-CSF) (1, 2). If the response to ESA/G-CSF is inadequate, the next step in therapy is regular transfusions (2). For patients with hypoplastic MDS, immunosuppressive therapy can be an option. For higher risk MDS therapeutic choices include hypomethylating agents (e.g. azacytidine) and low-dose chemotherapy (1). The only curable treatment is allogeneic transplantation, being an option for patients <70 years and higher risk MDS.

Treatment with ESA can improve anemia with an effect lasting on average two years (range 3-118 months) (7). Most patients with MDS will eventually require red cell transfusions (8). The many red cell transfusions given to these patients result in iron overload mainly attributed to reticulo-endothelial iron recycling (8) which causes an accumulation of iron in the tissue and results in damages mainly to the heart, liver and endocrine glands of the body (9, 10). Iron overload and its consequences is more thoroughly studied in thalassemia patients where studies have shown that iron overload can result in cardiomyopathy, liver cirrhosis, hypogonadism, hypothyroidism, diabetes due to iron deposition in the beta cells of the pancreas etc. (11-13). Iron chelation therapy allows us to chemically remove the iron from the body (14). Studies have shown that we can prolong the patient’s life and prevent organ complications with the use of iron chelation therapy (11, 13, 15). Hematologists today use this knowledge in the treatment of MDS (16-18).

The MDS Guideline Programme (2) states that only patients where long term transfusion therapy is likely are to be considered for iron chelation. For patients with refractory anemia (RA), refractory anemia with ring sideroblasts (RARS) and MDS associated with isolation deletion (5q-) iron chelation therapy is indicated unless the patient is of very high age or has severe concomitant disease. When it comes to refractory anemia with multilineage dysplasia
(RCMD) and more advanced MDS iron chelation should only be considered for patients with a life expectancy of at least 2 years from the time point where iron overload is reached. It is also recommended to chelate patients that are eligible for allogeneic stem cell transplantation (SCT). Iron chelation is recommended to start when S-ferritin exceeds 1500 µg/L or after approximately 25 red cell transfusions.

Seeing as the MDS population is elderly echocardiography is used in the monitoring of heart function, in both elderly and iron overloaded patients, to detect signs of congestive heart failure or other cardiac effects (5, 11, 13, 19). Cardiovascular T2-star magnetic resonance imaging (MRI) MRT2 * imaging can be used to monitor cardiac and liver iron overload (20, 21).

Today, we have three different drugs available for the treatment of iron overload; Deferiprone (Ferriprox®), Deferoxamine (Desferal®) and Deferasirox (Exjade®). All the drugs have disadvantages, either because of side effects or because of way of administration (22). As mentioned above active chelation therapy can prolong a patient’s life and prevent organ complications (15). For grown MDS-patients, however, we know (23) that many patients are iron overloaded without being chelated even though recent studies have indicated that there may be a survival advantage for MDS patients treated with iron chelation therapy (17, 18).

Transfusion dependency plays an important role in prognostics and overall survival in MDS why we have chosen to look specifically at this in our study. The higher number of transfusions per month; the worse the prognosis (24). These discoveries have resulted in an updated prognosis scoring system - the WPSS, which takes transfusion dependency into
consideration which the IPSS system does not (25). S-Ferritin levels are commonly used in the monitoring of potential iron overload (17, 23, 26) and recommended for this purpose (1, 2, 27).

Specific objectives

Our hypothesis is that transfusion dependent patients with lower risk MDS and iron overload are undertreated with chelating agents, due to rather unclear directions as to who shall receive this, and drugs that have many side effects.

Our specific aims were to:

- Identify all patients diagnosed and/or treated 2009-2014 at Sahlgrenska University Hospital with lower risk MDS.
- Identify how many patients in this population meet the criteria for iron chelation therapy.
- Identify how many patients that actually are given iron chelation therapy.
- Investigate how patients with and without chelation therapy were followed up.
- Investigate if there was any benefit in terms of transfusion dependency, S-ferritin and overall survival in the chelated patients compared to the patients that did not receive chelation therapy.

Material and Methods

Patients

All patients registered in the INCA-registry (Information Network for Cancer in Sweden) who were diagnosed with Myelodysplastic syndromes (MDS) at the Department of Hematology, Sahlgrenska University Hospital during 2009 and 2014 was the source of eligible patients for
the study. As chelation treatment mostly is used in patients with lower risk MDS, i.e. patients with an IPSS score of up to 1 point (Low and INT-1) (2), we defined our cohort to be lower risk MDS patients with a follow-up-time up to Dec 31st, 2014.

Data collecting procedures
Age, gender, date of MDS diagnosis, date of death and prognostic score for the patients was gathered from the INCA MDS registry. The patients’ electronic journals from Melior were the source of information about treatment, and blood values were read from the LabBest or FlexLab system. Serum-ferritin-levels were recorded at least once a year, if possible. The different types of therapy which the patients had been given for their MDS were registered. The different therapies were divided into groups; erythropoiesis stimulating agents (ESAs), Granulocyte – colony stimulating factors (G-CSF), immunosuppressive therapy (e.g. cortisone, cyclosporine, TNFα-inhibitors etc.), chemotherapy, azacytidine, red cell transfusions and iron chelation therapy. The number of months on therapy was recorded, as well as number of transfusions. Some patients underwent allogeneic SCT and the date of transplantation was registered.

According to the MDS Guideline Programme (2), the date when the patients reached either a level of S-ferritin of 1500 µg/L or had received ≥ 25 red cell transfusions was defined as the date when iron chelation was indicated. These factors were examined for all patients and the dates of indication were recorded for the patients who met the criteria regarding S-ferritin and/or number of transfusions. In this manner, two groups were created and studied closer (Table 3), both those who received chelation and those who fulfilled the criteria, but did not receive chelation. The patients who did not meet the above mentioned criteria or did not receive chelation therapy were not targets for further investigation.
The date of initiation of chelation therapy was recorded or date when the patients met the criteria of chelation therapy indication as mentioned above, referred to as date of indication. For the chelated patients, the time (in months) on chelation therapy was recorded. Endpoints were set as time of death or December 31st 2014 as censoring date for the patients still alive.

In order to see if the number of transfusions decreased after initiation of chelation therapy, the number of transfusions given during the three months prior to either initiation of chelation therapy or to the date of indication as mentioned above was compared to transfusion dependency during the six months following after initiation of chelation or date of indication. The total number of transfusion given from diagnosis to death or censoring date was recorded for all patients.

The Serum-ferritin (S-ferritin) was used as a marker for iron overload. For both chelated and non-chelated patients the S-ferritin level was recorded at time for start of chelation or the time that the criteria for chelation were fulfilled and as close to six months later as possible in order to see if the chelation therapy had any impact on the S-ferritin level. In the cases where there were no S-ferritin samples taken within six months of the desired time points no S-ferritin levels were recorded.

Additional indicators of iron overload were elevated liver transaminases (S-ALT and S-AST). A doubling of the upper limit of reference range was considered to be pathological for liver transaminases i.e. S-ALT ≥ 1.5 µg/L and S-AST ≥ 1.2 µg/L according to the reference ranges of the Sahlgrenska University Hospital laboratory. We also wanted to see how many patients
that had performed echocardiography in order to find signs of congestive heart failure recorded as reduced left ventricular ejection fraction (LVEF).

Mean and median survival date of reached indication for the chelation and non-chelation group were obtained respectively and the groups were compared. Survival from diagnosis for all patients was recorded.

Statistical methods
To examine significance in the differences in transfusion dependency for the two groups between the two time points Independent-Samples T-test was performed. This method was also used to examine the differences in S-ferritin for the two time points. To depict survival the Kaplan-Meier method was used and the Log Rank/Mantel-Cox test was used to examine the significance of the difference between the Kaplan Meier curves. The Cox regression analysis for the factor Treatment i.e. chelation vs non-chelation was used to further examine the differences in survival. Seeing as our material was rather small a 4x4 crosstab was created regarding occurrence of events and the Fisher’s exact test was performed to examine the statistical significance between the two groups. All statistical analyses were performed in IBM SPSS Statistics 22.

Ethics
This project was a student project and considered a work of improvement; hence it was not necessary for us to apply for admission from the ethical board. The project required us to read the medical records of living as well as deceased patients. When doing so we used methods to keep the confidentiality of the patients by unidentifying them as well as keeping all documents regarding their data in encrypted files with password protection.
Results

Patients
In total 169 patients diagnosed with MDS were found in the INCA registry from Sahlgrenska University hospital in the period 2009-14. After the exclusion of 100 patients due to different (Table 3), 69 patients were eligible as the study population.

Twenty-seven out of 69 patients fulfilled the criteria for receiving chelation therapy i.e. received at least 25 red cell transfusions and/or having a S-ferritin of at least 1500 µg/L. Out of these 27 patients there were nine patients who actually had been given chelation therapy (chelated group) while the remaining 18 patients never had received chelation therapy (non-chelated group).

The median age of the patients in the chelated group was 72 years at diagnosis compared to 75 years in the non-chelated group (see Table 4). There was also a larger fraction of patients with Low IPSS (=IPSS score 0) in the chelated group, three out of nine patients (33 percent) compared to four out of 18 patients (22 percent) in the non-chelated group.

When comparing the different regimes of treatment in the two groups it was evident that the group which eventually received chelation therapy were more often given ESAs, G-CSF, Azacytidine as well as immunosuppressive therapy (Table 4). Four patients in the non-chelated group underwent allogeneic SCT due to transformation to AML whereas no patient in the chelated group was transplanted.

Transfusions
Figures 1a and 1b depict the transfusion dependency over time in the two groups. The mean difference in transfusions between three months prior to start of chelation and six months after
was an increase in 0.4 transfused units per months, (median 0.3 transfused units per month) in the chelated group compared to a mean difference of 0.2 transfused units per month (median 0 transfusions per month) in the non-chelated group.

Thereby transfusion dependency increased over time in both groups but the difference between the groups was not statistically significant (P=0.883).

Ferritin levels
The levels of ferritin decreased clearly in the chelated group (see Figure 2a) with a mean difference of approximately -980 µg/L between the start of chelation therapy and six months later. The median level of ferritin at the first measurement was 3400 µg/L and 2100 µg/L at the second measurement. We could also see that the inter-individual variance was large and could also see that there was a trend towards aggregation at a level close to the 1500 µg/L which is the level where chelation therapy is indicated. A majority (five out of nine patients) ended up with a ferritin level between 1100 and 2100 µg/L.

As for the non-chelated group we noticed that the follow-up of S-ferritin was not as thorough. Out of the entire group of 18 patients, only six patients had S-ferritin levels monitored relatively close to the date of reached indication and six months later. We have chosen to only include these six patients in the tables regarding this (Figure 2b). The mean difference between the two time points was an increase of approximately 480 µg/L of ferritin. The median level of ferritin at the first measurement was 1650 µg/L and 1900 µg/L at the second measurement. Although the figures show a clear difference in this small sample there was no statistical significance between the groups (P=0.107).
Monitoring of iron overload in liver and heart

Regarding the additional monitoring of iron overload all chelated patients had undergone examination of liver transaminases and six out of nine patients had undergone echocardiography. None of these patients showed signs of congestive heart failure. Eight of nine patients (89 percent) had elevated levels of ALT or both ALT and AST at least once from MDS diagnosis. In the non-chelated group, 16 out of 18 patients (89 percent) had undergone examination of liver transaminases and in 9 out of 18 patients (50 percent) echocardiography was performed. Eight patients had elevated levels of ALT or ALT and AST at least once from MDS diagnosis. One patient had congestive heart failure in this group, but this was due to aortic stenosis and not to iron overload. No patient was examined with MRI T2* in order to evaluate iron overload.

Survival

The overall survival seemed to be better in the chelated group. The median total duration of illness (survival time from diagnosis) was approximately 46 months in the chelated group (mean 42 months) as compared to approximately 30 months (mean 30 months) in the non-chelated group. We examined the difference between the two groups by comparing survival from date of reached indication in both groups. This resulted in a median survival of approximately 23 months (mean 29 months) in the chelation group compared to 10 months in the non-chelated group (mean 12 months). The data also shows that a majority (five out of nine) of the chelated patients were still alive at the end of study.

The Kaplan-Meier curve (Figure 3) showed a statistically significant difference between the two groups, (P=0.045). The Cox regression analysis for difference between the groups was borderline significant, P=0.058.
Discussion

We have studied patients diagnosed with low risk MDS, identified the population that fullfilled the criteria for iron chelation due to iron overload and compared patients that did or did not receive chelation therapy.

Generally, we can say that no statistical significance between the groups was seen in the differences in both transfusion dependency and S-ferritin but there was a clear difference in overall survival. This could be a result of several different factors, such as age, co-morbidities, more aggressive disease but may also be a result of inadequate therapy in the non-chelated group.

The patients in the chelated group were given more treatment for their MDS disease, with higher numbers of patients treated with the first line of therapy; ESA and G-CSF. The chelated group was also given azacytidine and immunosuppressive treatment to a greater extent than the non-chelated group. The fact that more patients in the non-chelated group were given chemotherapy and underwent SCT (no patient in the chelated group) was mainly due to transformation into acute myeloid leukemia (AML), indicating that this patient group, although regarded as lower risk patients, had a more aggressive disease. This occurred in five patients (28 percent) in the non-chelated group whereas only one patient transformed to AML in the chelated group. We are uncertain why this was the case but it has previously been suggested that chelation therapy reduces the risk of MDS progression to AML (28) and studies on cell lines have also showed that chelation therapy could have anti-proliferative effects on several different cell-lines including myeloid cell-lines (29, 30) as well as potentiate anti-neoplastic activity in cells (31).
Regarding transfusion dependency, we saw that both groups increased their average number of transfusions per month between the two time points of investigation as mentioned above. There was no statistical significance between the groups (P=0.883, not significant) hence we cannot draw any conclusions regarding transfusion dependency in this study. We see, though, in actual figures that the mean number of transfusions given per month was higher at both time points in the non-chelated group. This may have had an impact on the overall survival of the groups as transfusion dependency is clearly viewed as a prognostic factor for overall survival (17, 24, 25) and is taken into consideration in the WPSS scoring system as mentioned above (25).

When examining the difference in S-ferritin it was obvious that the monitoring of the non-chelated patients was not as thorough as for the chelated patients. Only six out of 18 patients had ferritin samples that we could analyze in this way even though these patients had been given at least 25 red cell transfusions or had S-ferritin-levels over 1500 µg/L. This is not unusual, at least one previous study has shown the same pattern (17).

We could see that the S-ferritin levels decreased in the chelated group (mean decrease 980 µg/L) whereas the ferritin levels increased in the non-chelated group (mean increase 480 µg/L). Previous retrospective studies have shown no decrease in ferritin after start of chelation therapy (32) yet interventional trials have shown significant reductions in ferritin (33, 34) why it is difficult for us to draw any conclusions on our own results. The results in our study are not statistically significant (P=0.107) but we might interpret the results as a trend towards a better effect of decreasing ferritin levels with chelation therapy, at least in this study.

Additional markers of iron overload as liver transaminases and echocardiography were also
more closely monitored in the chelated group. A higher percentage of the chelated patients had elevated transaminases during some point in the course of the disease which could indicate a higher degree of iron overload. This pattern could also be seen in the generally higher S-ferritin levels of the chelated group (Figures 2a and 2b). As mentioned above only one patient showed pathologic values of ejection fraction which was attributed to stenosis of the aortic valve and not due to iron overload.

The survival from date of indication for both groups was compared i.e. different time points than the other factors. The median difference between the groups was approximately 13 months (P=0.045, see Figure 3). The median age of the patients in the chelated group was higher than in the non-chelated group. We interpreted the fact that a majority of the chelated patients still alive at the end of the study a positive prognostic factor too. Age has been shown to have an effect on overall survival in several studies and especially in the patients with lower risk MDS (24, 25). The larger fraction of patients with a “Low IPSS score” in the chelated group could also have an impact on the better overall survival in this group.

Since we have not adjusted for age, IPSS and co-morbidities in the study we can only consider our results as an indication that chelation therapy may prolong survival in heavily transfused MDS patients, similar to the results of several recent studies that have suggested that chelation therapy can be regarded as an independent positive prognostic factor for overall survival in heavily transfused MDS patients (17, 23, 32, 35).

One very possible bias in this study is the clinicians’ decision of treatment and potential chelation therapy might be that the clinicians decide on beforehand which patients they believe have better chance of survival and therefore choose therapy (first line, second line etc.
and eventually also chelation therapy) with this taken into consideration. This possible bias has also been discussed in other previous articles (17, 23).

Another general observation is that only a portion of the patients eligible for chelation have been given chelation therapy. We consider this due to elderly patients, expensive drugs, the known side effects as well as vague guidelines. Another interesting remark is that two of the non-chelated patients had a clear iron overload at the time point of their stem cell transplant even though the MDS Guideline Programme states that iron overload should be avoided in candidates for stem cell transplant and therefore iron chelation therapy should be considered to prevent iron overload in these patients (2).

One clear weakness with our study is of course the limited material and amount of patients included as well as the lack of multivariate analysis including e.g. adjustment for age and co-morbidities. Another weakness is the use of different time points when comparing different factors. On the other hand, one of the strengths of the study is that seeing as the study population was rather small we have been able to follow every patient’s course of disease closely, and have had time to scrutinize the patients’ electronic journals. Thereby we have been able to extract many different factors and information regarding each patient.

Conclusions and Implications

Regarding transfusion dependency we could not see any significant benefits with chelation therapy. Regarding overall survival we believe our results may indicate that chelation therapy could be beneficial for heavily transfused MDS patients as it has been suggested in several recent retrospective studies. One randomized study presented at ASH 2015 (The 57th American Society of Hematology Annual Meeting and Exposition) (36) indicates that
chelation can be beneficial to patients with lower risk MDS regarding survival, but further randomized studies are warranted.

In conclusion, we want to illuminate the need of clearer guidelines regarding iron chelation therapy seeing as many patients at our clinic have not been given chelating agents even though several studies have shown improved survival as well as other benefits with this treatment.

**Populärvetenskaplig sammanfattning på svenska**

**Järninlagring och kelatbehandling hos patienter med lågrisk myelodysplastiskt syndrom**

Myelodysplastiskt syndrom (MDS) är en grupp blodsjukdomar som kännetecknas av att benmärgen tappar förmågan att tillverka röda blodkroppar, vita blodkroppar eller blodplättar på rätt sätt. Detta gör att patienterna dels får blodbrist (anemi) och därmed får svårare att transportera syre, dels får svårt att tackla eventuella infektioner alternativt blir blödningsbenägna. Utifrån en rad variabler, bl a blodvärden, genetiska förändringar och förekomst av omogna celler delar man in sjukdomarna in i ”lägre risk” och ”högre risk” (för övergång i akut leukemi eller att avlida av sjukdomen). För patienter med lågrisk MDS består behandlingen ofta i blodtransfusioner (blodöverföring) för att höja blodvärden. Många blodtransfusioner innebär risken att man även får för mycket järn som kroppens celler lagrar in vilket kan ge komplikationer såsom hjärt- och leversvikt.

Så kallad kelatbehandling/kelering kan användas för att ta bort järnet ur kroppen. Järnet binds genom en kemisk reaktion och skiljs ut genom urin eller avföring. Tyvärr finns inga bra
studier för denna patientgrupp som har visat att kelatbehandling hjälper, däremot finns studier för andra grupper av patienter med anemi sedan födseln där behandlingen har god effekt. Kelatbehandling rekommenderas därför till patienter som får regelbundna blodtransfusioner, har höga ferritin-värden ("depåjärn") och som dessutom förväntas leva mer än två år. Läkemedlen är dyra och kan ha svåra biverkningar varför vissa läkare drar sig för att använda dem.


Mängden mottagna blodpåsar samt patienternas ferritin-värden jämfördes med samma värden för den grupp med 18 patienter som enligt riktlinjerna borde fått kelatbehandlingen men som av olika skäl inte fick den. Några statistiskt säkerställda skillnader mellan mängden givet blod kunde inte ses, däremot sågs en trend mot att de patienter som fick kelatbehandling fick lägre ferritin-värden medan övriga patienter istället fick högre värden av ferritin under motsvarande period. Överlevnaden jämfördes mellan grupperna och man konstaterade att patienterna som fick kelering levde i genomsnitt 13 månader længre än de patienter som inte fick behandlingen.

Patienterna med kelatbehandling blev dessutom mer noggrant övervakade vilket skulle kunna vara en fingervisning om att läkarna på förhand, medvetet eller omedvetet, väljer ut vilka patienter som skall ”satsas på”.
Mängden patienter i studien är liten varför man ej kan dra stora slutsatser av resultaten.
Vidare har det ej justerats för ålder och samsjuklighet vid jämförelse av överlevnad mellan grupperna. En styrka med studien är dock att man kunnat granska varje enskild individ i studien noggrant.

Resultaten från studien går i linje med från tidigare studier som tyder på en överlevnadsfördel med kelatbehandling men för att fastställa detta krävs större s.k. prospektiva, dvs framåtblickande studier.

Studien visar att för få patienter mellan 2009 och 2014 har fått kelatbehandling och att det därför behövs tydligare riktlinjer då dagens riktlinjer inte verkar räcka till för att alla ska få den behandling de behöver.

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References


Tables and Figures

Table 1. The WHO 2008 Classification of Myelodysplastic syndromes

<table>
<thead>
<tr>
<th>Myelodysplastic syndromes:</th>
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<tbody>
<tr>
<td><strong>“Lower risk”:</strong></td>
</tr>
<tr>
<td>Refractory anemia (RA)</td>
</tr>
<tr>
<td>Refractory neutropenia (RN)</td>
</tr>
<tr>
<td>Refractory thrombocytopenia (RT)</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts (RARS)</td>
</tr>
<tr>
<td>Refractory anemia with multilineage dysplasia (RCMD)</td>
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<td>MDS associated with isolation deletion (5q-)</td>
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<td><strong>“Higher risk”:</strong></td>
</tr>
<tr>
<td>Myelodysplastic syndrome – unclassified (MDS-U)</td>
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<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
</tr>
</tbody>
</table>

Mixed MDS/MPN:
Chronic myelomonocytic leukaemia (CMML)
Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)
Juvenile myelomonocytic leukaemia (JMML)
Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN)
Refractory anaemia with ring sideroblasts associated with marked
thrombocytosis (RARS-T) (provisional entity)2

Table 2, IPSS-score

The table describes how to calculated the IPSS-score which is the most commonly used
scoring system for prognostics regarding Myelodysplastic Syndromes.

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
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<tr>
<td></td>
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<td>BM blasts (%)</td>
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</tbody>
</table>

*Good:normal,-Y,del(5q),del(20q). Poor: complex (>3 abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities. ‡Hemoglobin <100 g/l, ANC <1.5 x 10^9/l, platelets <100 x 10^9/l.

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥2.5.

Abbreviations: IPSS, International Prognostics Scoring System; BM, Bone marrow; ANC, absolute neutrophil count; INT-1, Intermediate-1; INT-2, Intermediate-2
Table 3, Patient Selection

The number of patients with MDS at Sahlgrenska 2009-2014, as well as the number of patients excluded from the study for each of the following reasons as shown in the left column, generating the study population.

<table>
<thead>
<tr>
<th>All patients with MDS at Sahlgrenska 2009-14 according to the INCA-MDS-registry:</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IPSS available</td>
<td>13</td>
</tr>
<tr>
<td>IPSS ≥ 1.5:</td>
<td>42</td>
</tr>
<tr>
<td>MDS/MPN:</td>
<td>30</td>
</tr>
<tr>
<td>Secondary MDS:</td>
<td>3</td>
</tr>
<tr>
<td>Treated outside the region:</td>
<td>3</td>
</tr>
<tr>
<td>Severe comorbidities:</td>
<td>2</td>
</tr>
<tr>
<td>other malignacies:</td>
<td>2</td>
</tr>
<tr>
<td>not fulfilling MDS criteria:</td>
<td>4</td>
</tr>
<tr>
<td>non-correlating transfusions and S-ferritin</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients theoretically eligible for chelation therapy: 69

Abbreviations: INCA, Informationsnätverk för cancervården (Information Network for Cancer Care); MDS, Myelodysplastic Syndrome; IPSS, International Prognostic Scoring System; MDS/MPN, Mixed Myelodysplastic Syndromes/Myeloproliferative Neoplasms

Table 4, Demographics, diagnosis, IPSS-score and therapy

Presentation of the variations in demographics, diagnosis, IPSS-score and therapy for the 27 patients who met the criteria for receiving chelation therapy and hence studied closer in the study.

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean N=27</th>
<th>%</th>
<th>Chelated N=9</th>
<th>%</th>
<th>Non-chelated N=18</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Median N=27</td>
<td>%</td>
<td>Chelated N=9</td>
<td>%</td>
<td>Non-chelated N=18</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>male N=27</td>
<td>%</td>
<td>Chelated N=9</td>
<td>%</td>
<td>Non-chelated N=18</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>RA</td>
<td>RARS</td>
<td>RCMD</td>
<td>5q-</td>
<td>MDS-U</td>
<td>RAEB-1</td>
</tr>
<tr>
<td>-----------</td>
<td>----</td>
<td>------</td>
<td>------</td>
<td>-----</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>25.9</td>
<td>3</td>
<td>33.3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>RA</td>
<td>1</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>RARS</td>
<td>2</td>
<td>7.4</td>
<td>1</td>
<td>11.1</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>RCMD</td>
<td>19</td>
<td>70.4</td>
<td>6</td>
<td>66.7</td>
<td>13</td>
<td>72.2</td>
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<tr>
<td>5q-</td>
<td>3</td>
<td>11.1</td>
<td>1</td>
<td>11.1</td>
<td>2</td>
<td>11.1</td>
</tr>
<tr>
<td>MDS-U</td>
<td>2</td>
<td>7.4</td>
<td>1</td>
<td>11.1</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>1</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5.6</td>
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<tr>
<td>IPSS</td>
<td>Low</td>
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<td>25.9</td>
<td>3</td>
<td>33.3</td>
<td>4</td>
</tr>
<tr>
<td>Int-1</td>
<td>20</td>
<td>74.1</td>
<td>6</td>
<td>66.7</td>
<td>14</td>
<td>77.8</td>
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<tr>
<td>Therapy</td>
<td>ESA</td>
<td>10</td>
<td>37.0</td>
<td>6</td>
<td>66.7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>G-CSF</td>
<td>9</td>
<td>33.3</td>
<td>6</td>
<td>66.7</td>
<td>3</td>
</tr>
<tr>
<td>Transfusions</td>
<td>27</td>
<td>100</td>
<td>9</td>
<td>100</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>Chelation</td>
<td>9</td>
<td>33.3</td>
<td>9</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Azacytidine</td>
<td>5</td>
<td>18.5</td>
<td>2</td>
<td>22.2</td>
<td>3</td>
<td>16.7</td>
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<tr>
<td>Immunosuppressive therapy</td>
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<td>44.4</td>
<td>5</td>
<td>55.6</td>
<td>7</td>
<td>38.9</td>
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<tr>
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<td>Chemotherapy</td>
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<td>37.0</td>
<td>3</td>
<td>33.3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Stem cell transplant</td>
<td>4</td>
<td>14.8</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Abreviations: RA, Refractory anemia; RARS, Refractory anemia with ring-sideroblasts; RCMD, Refractory cytopenia with multilineage dysplasia; 5q-, Myelodysplastic syndrome associated with isolated del(5q); MDS-U, Myelodysplastic syndrome, unclassifiable; RAEB-1, Refractory anemia with excess blasts 1; RAEB-2, Refractory anemia with excess blasts 2; ESA, Erythropoietin stimulating agents; G-CSF, Granulocyte-colony stimulating factor.
**Fig 1a**: Transfusion dependency (mean number of transfusions given per month) shown for the chelated patients. The mean difference between the three months prior to start of chelation therapy and the six months following after start of chelation therapy was an increase in 0.3 red cell transfusions per month (median 0.4). The figure displays the individual variance between the two time periods.

**Fig 1b**: Transfusion dependency shown for the non-chelated patients. The mean difference between the three months prior to the date when each patient reached the indication for chelation therapy (in our study when the patient reached 25 red cell transfusions or had a S-ferritin of at least 1500 µg/L) and the six months following the date of reached indication was 0.2 months (median 0). When comparing the mean difference between the two groups (chelated and non-chelated patients) there was no statistical significance (P=0.883).

**Figure 2a**: Ferritin levels before and after chelation, chelated patients.

**Figure 2b**: Ferritin levels before and after date of reached indication, non-chelated patients.
**Fig 2a** Ferritin levels before and after initiation of chelated therapy shown for the chelated patients. There as a mean decrease in ferritin levels of 980 µg/L between the start of chelation therapy and six months later. No statistical significance was seen between the groups (P=0.107).

**Fig 2b** Ferritin levels before and after date of reached indication for chelation therapy for the non-chelated patients. Only six of the non-chelated patients had ferritin values that from the examined time points. In these six patients there was a mean increase in ferritin levels of 480 µg/L between the time point where they should have been offered chelation therapy (according to the guidelines) i.e. date of reached indication for chelation therapy, and six months later. No statistical differences was seen between the groups (P=0.107).

**Figure 3,** Cumulative survival displayed as Kaplan-Meier curve

The Kaplan-Meier curve depicts the difference in cumulative survival from the date of reached indication (for chelation therapy) between the chelated and the non-chelated patients. The median time between date of reached indication to death or end of study was 23 months for the chelated patients. As for the non-chelated patients the median time between the date of reached indication and death or end of study was only 10 months. The Log Rank (Mantel-Cox) value shows that the differences were statistically significant (P=0.045).

<table>
<thead>
<tr>
<th>Overall comparisons</th>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>4.025</td>
<td>1</td>
<td>.045</td>
</tr>
<tr>
<td>Breslow (Generalized Wilcoxon)</td>
<td>5.375</td>
<td>1</td>
<td>.020</td>
</tr>
<tr>
<td>Tarone-Ware</td>
<td>4.892</td>
<td>1</td>
<td>.027</td>
</tr>
</tbody>
</table>