# Myelodysplastic Syndromes Over Time: A Comparison of Two Patient Cohorts

Howard S. Oster MD PhD[1,3], Shani Svorai-Litvak MD[1,3], Ilya Kirgner MD[2,3], Albert Kolomansky MD[1,3], Robert S. Siegel MD[4] and Moshe Mittelman MD[1,2,3]

Departments of [1]Medicine A and [2]Hematology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Department of Hematology–Oncology, George Washington University Medical Center, Washington, DC, USA

**ABSTRACT:** **Background:** With advances in myelodysplastic syndromes (MDS), patient cohorts from different time periods might be different.

**Objectives:** To compare presentation and outcomes between two cohorts.

**Methods:** Data were collected from George Washington University Medical Center, Washington, DC, USA 1986–1987 (DC), and Tel Aviv Medical Center, Israel 1999–2009 (TA).

**Results:** The study comprised 227 patients (139 TA, 88 DC). TA patients were older (75.4 ± 9.8 vs. 63.8 ± 14.3 years, $P < 0.001$) and had more cardiovascular diseases (56.8% vs. 14.8%, $P < 0.001$), fewer cytopenias (1.67 ± 0.82 vs. 2.0 ± 0.93, $P = 0.003$), and lower mean corpuscular volume (94.3 ± 9.9 fl vs. 100.5 ± 15.3 fl, $P < 0.001$). Hemoglobin, leukocyte, neutrophil, and platelet counts were similar. More TA patients had dysplasias. Bone marrow cellularity and cytogenetics were similar, but more TA patients had blasts < 5% (73.4% vs. 50.6%, $P = 0.003$). More TA patients had early French-American-British (FAB) disease (66.9% vs. 40.9%, $P < 0.001$) and lower risk disease per International Prognostic Scoring System (81% vs. 50%, $P < 0.001$). The 5 year survival (5YS) of TA patients was not significantly greater (62% vs. 55%). 5YS by FAB was also slightly greater for TA patients (77% vs. 65% for early FAB; 43% vs. 37% for advanced FAB, $P > 0.05$).

**Conclusions:** Although patients diagnosed with MDS at a later period were older and had more cardiovascular co-morbidities, they had fewer cytopenias, tended to have earlier disease, and had minimally greater, but not significant, 5YS.

*IMAJ* 2018; 20: 608–612

**KEY WORDS:** myelodysplastic syndromes (MDS), patient cohorts, retrospective cohort study, survival analysis

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal bone marrow disorders characterized by abnormal differentiation and maturation, leading to peripheral blood cytopenias, functional defects, and potential leukemic transformation [1,2]. Over the last decades, significant progress has been made in understanding the genetics and biology of the disease, as well as improving techniques for early diagnosis and developing novel therapeutic approaches [3,4]. These developments have raised questions about the differences in patients treated in the 2000s as opposed to those from the 1980s. Are their disease features different from what they used to be? Is the outcome of MDS patients better now? This study compares two patient cohorts from different time periods in an attempt to answer these questions.

## PATIENTS AND METHODS

Two patient cohorts were compared and retrospectively analyzed. The first cohort included 88 consecutive MDS patients followed and/or treated from January 1986 through December 1987, at the George Washington University Medical Center and the Veterans Administration Hospital, which is affiliated with the university medical center. Both of these institutions are located in Washington, DC, USA. This patient group (DC) represents a cohort from the 1980s. The second cohort included 139 consecutive transfusion-dependent MDS patients, who were treated at the Blood Bank and Hematology Division at Tel Aviv Sourasky Medical Center from December 1999 through December 2009 [5]. This group (TA) represents a more recently treated group from a country where treatment protocols are similar to those used in the United States. Both hospitals are tertiary medical centers.

We reviewed the records of the patients and retrospectively collected relevant epidemiological, demographic, clinical, laboratory, and prognostic parameters at presentation in addition to survival data. The analyzed data included patient age, gender, and co-morbidities, as well as hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell (WBC) count, absolute neutrophil count (ANC), platelet count, routine blood chemistry especially serum creatinine and lactic dehydrogenase (LDH) levels, serum iron, transferrin and ferritin, bone marrow (BM) cellularity, erythroid, myeloid and megakaryocytic dysplasia, blast percentage, cytogenetics, and French-American-British (FAB) [6] and International

Prognostic Scoring System (IPSS) [7] classifications subgroup distribution. The cumulative 5 year overall survival (5YS), defined as the duration between diagnosis and death, was assessed as well.

We did not address the specific treatments that the patients had received; however, as of the time of this analysis, the TA (recent) patients had not yet been treated with novel agents.

Institutional review board committees from both institutions approved the study, with de-identified data.

### STATISTICAL METHODS

The results for the different continuous parameters are presented as mean ± standard deviation (SD). To evaluate the differences in the two groups, the *t*-test was used. For categorical parameters, we used proportions. Chi square and Fisher's exact tests were applied to evaluate their differences. To check for a difference in survival, we first used the Kaplan–Meier model and then the Cox regression model after controlling for the statistically significant confounding effects (number of cytopenias, FAB subgroup, and age). Statistical analyses were performed using Statistical Package for the Social Sciences software version 18 (SPSS Inc., Chicago, IL, USA).

**Table 1.** Patient characteristics

| | TA patients | DC patients | *P* |
|---|---|---|---|
| **Number** | 139 | 88 | – |
| *Age, years (mean ± SD) | 75.4 ± 9.8 | 63.8 ± 14.3 | ‹ 0.001 |
| Males | 61.2% | 68.2% | 0.322 |
| **Co-morbidities** | | | |
| *Cardiovascular disease | 56.8% | 14.8% | ‹ 0.001 |
| Cancer | 11.5% | 6.8% | 0.357 |
| Renal | 7.2% | 1.1% | 0.054 |
| **Laboratory Values** | | | |
| Hemoglobin, g/dl | 9.88 ± 1.7 | 10.05 ± 2.7 | 0.544 |
| Hematocrit | 29.1 ± 5.3% | 29.7 ± 7.6% | 0.534 |
| *MCV, fl | 94.3 ± 9.9 | 100.5 ± 15.3 | ‹ 0.001 |
| WBC, ×109/L | 7.19 ± 6.4 | 7.87 ± 11.7 | 0.570 |
| *Neutrophils | 53.5% | 46.8% | 0.007 |
| ANC, ×109/L | 4.18 ± 4.7 | 3.65 ± 5.4 | 0.438 |
| Platelet, ×109/L | 176.8 ± 139 | 185.7 ± 215 | 0.706 |
| *Cytopenias, number | 1.67 ± 0.82 | 2.0 ± 0.93 | 0.003 |
| *Creatinine, mg/dl | 1.35 | 1.87 | 0.014 |
| *LDH, u | 497.4 | 266.5 | ‹ 0.001 |
| *Iron, mcg/dl | 87.4 | 132.9 | 0.003 |
| Transferrin, mg/dl | 193.5 | 245.2 | 0.117 |
| Ferritin, ng/ml | 315.7 ± 340 | 451.2 ± 424 | 0.298 |

*Characteristics with significant difference in groups

TA = patients from Tel Aviv, Israel (1999–2009), DC = patients from Washington, DC, USA (1986–1987)

LDH = lactic dehydrogenase, MCV = mean corpuscular volume, WCB = white blood cell

## RESULTS

In total, 227 MDS patients were analyzed: 139 patients in the TA group, and 88 in the DC group. Table 1 summarizes the patient characteristics. TA patients were older (75.4 ± 9.8 years) than the DC patients (63.8 ± 14.3 years, $P < 0.001$) but the gender distribution was similar in both groups.

At presentation, 56.8% of the TA patients were diagnosed with cardiovascular disease, significantly more than the DC patients (14.8%, $P < 0.001$). More TA patients (11.5% vs. 6.8%) had a second malignancy, although not statistically significant ($P = 0.357$). More TA than DC patients (7.2% vs. 1.1%) were diagnosed with renal disease with a borderline significance ($P = 0.054$). The incidence of other co-morbidities was similar in both groups (data not shown).

The routine laboratory values at presentation are shown in Table 1. Hemoglobin, hematocrit, WBC, ANC, and platelets were similar in both patient groups. Neutrophil percentage was higher in the TA patients but since ANC was similar, there is no clinical significance to this difference. Two hematological parameters were significantly different. At presentation TA patients had fewer cytopenias than DC patients, 1.67 vs. 2.02 ($P = 0.003$) and TA patients had less macrocytosis, with a lower MCV, 94.3 fl, compared with 100.5 fl in DC patients ($P < 0.001$). Serum creatinine was significantly lower and LDH was significantly higher in TA patients. Serum iron was lower in TA patients (87.4 µg/dl vs. 132.9 µg/dl, $P = 0.003$), but serum transferrin and ferritin were similar in both patient groups. Other routine chemistry values were similar in both groups (data not shown).

The BM findings are summarized in Table 2. BM cellularity was similar in both patient groups. However, more TA than DC patients were found to have erythoid, myeloid, and megakaryocytic dysplasias.

Interestingly, despite the higher incidence of such dysplasias among TA patients, more patients from this group (74.3% vs.

**Table 2.** Bone marrow cellularity was similar in both patient groups. TA patients had more dysplasias but lower blast counts (more TA patients had ‹ 5% blasts)

| | TA patients, % | DC patients, % | *P* |
|---|---|---|---|
| **Bone marrow cellularity** | | | |
| Normocellular | 24.5 | 31.0 | 0.47 |
| Hypocellular | 20.9 | 16.1 | |
| Hypercellular | 54.7 | 52.9 | |
| **Dysplasia** | | | |
| Dyserythropoiesis | 79.9 | 71.3 | 0.005 |
| Myelodysplasia | 63.3 | 52.9 | 0.003 |
| Dysmegakaryopoiesis | 53.2 | 40.2 | 0.001 |
| **Blast count (%)** | | | |
| ‹ 5 | 74.3 | 50.6 | 0.003 |
| 5–10 | 16.5 | 24.1 | |
| 10–20 | 7.2 | 17.2 | |
| 20–30 | 2.9 | 8.0 | |

TA = patients from Tel Aviv, Israel (1999–2009), DC = patients from Washington, DC, USA (1986–1987)

50.6%) were classified as having an earlier (< 5% BM blasts) MDS disease. DC patients, despite less BM dysplasia, were diagnosed as having a more advanced disease with a higher BM blast percentage. Of note, as expected, the percentage of patients with missing data on dysplasia was significantly lower in the TA group as opposed to the DC patients. Only in 1.4% of TA patients were data missing on erythroid, 2.2% on myeloid, and 3.6% on megakaryocytic dysplasia, while the percentages of patients with missing data in the DC group were 11.5%, 13.8%, and 17.2%, respectively. Cytogenetics by G-banding in those patients for whom the data were available were similar in both groups (data not shown).

Prognostic classifications are presented in Table 3. Since more TA patients had a lower BM blast count, more patients from this group were classified as having early disease, i.e., refractory anemia or refractory anemia with ring sideroblasts (RA/RARS) FAB subtypes (66.9% in the TA group vs. 40.9% in the DC group, respectively). In the DC group, more patients were classified in the advanced FAB subgroup (RAEB/RAEB-t/CMML) 59.1% DC vs. 33.1% TA). These differences were statistically significant ($P < 0.001$).

IPSS status could be determined in only 131 patients from the whole cohort of both patient groups, with 89 patients classified as low risk or intermediate-1 IPSS, and 42 patients were classified as intermediate-2 or high risk [Table 3]. Consistent with the FAB findings, TA patients tended to be mostly low risk according to IPSS (61/75 patients [81.3%] vs. 28/56 [50%] in the DC group, $P < 0.05$). The reciprocal picture for high-risk MDS distribution at diagnosis was only 14 patients (18.7%) in the TA group vs. 28 patients (50%) in the DC group. These differences were also statistically significant ($P < 0.001$).

The cumulative 5 year survival (5YS) was calculated by Cox regression analysis after controlling for confounding effects [Table 3, Figure 1A, Figure 1B]. The 5YS was 62% for the TA group vs. 55% for the DC patients, not a statistically significant difference [Table 3, Figure 1A]. The 5YS according to FAB

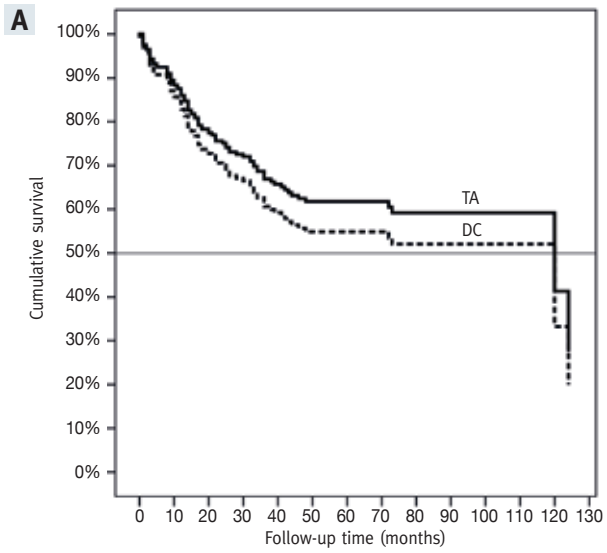
**Table 3.** Patient classification and prognosis
More TA patients had early (favorable) MDS: RA/RARS according to the FAB classification and LR-MDS according to the IPSS classification

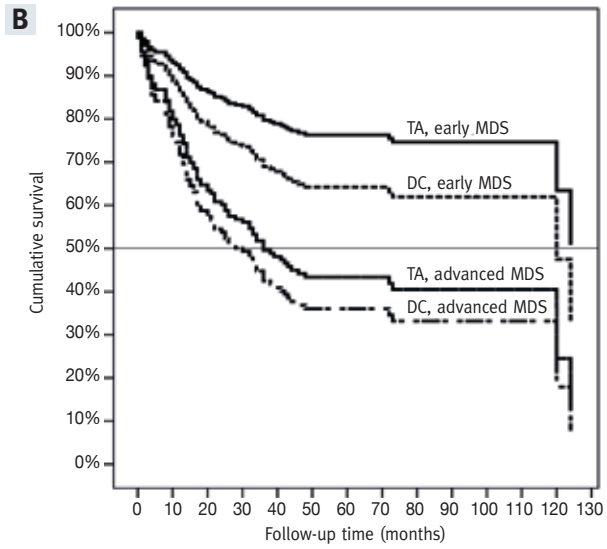
| | TA patients (%) | DC patients (%) | *P* |
|---|---|---|---|
| **FAB (n=227)** | 139 patients | 88 patients | |
| Early (n=129) | 93 (66.9) | 36 (40.9) | ‹ 0.001 |
| Advanced (n = 98) | 46 (33.1) | 52 (59.1) | |
| **IPSS (n=131)** | 75 patients | 56 patients | |
| Lower risk (n=89) | 61 (81.3) | 28 (50) | ‹ 0.001 |
| Higher risk (n=42) | 14 (18.7) | 28 (50) | |
| **5 year survival, %** | | | |
| Cumulative 5YS | 62 | 55 | NS |
| **FAB 5YS** | | | |
| RA/RARS | 77 | 65 | NS |
| Advanced | 43 | 37 | NS |

TA = patients from Tel Aviv, Israel (1999–2009), DC = patients from Washington, DC, USA (1986–1987)

5YS = 5 year survival, advanced = RAEB/RAEB-t/CMML, early = RA/RARS, FAB = French-American-British, HR = higher risk (Int-2/high), IPSS = International Prognostic Scoring System, LR = lower risk (Low/Int-1), MDS = myelodysplastic syndromes, NS = non-significant, RA/RARS = refractory anemia/refractory anemia with ring sideroblasts

**Figure 1.** Prognosis: cumulative 5 year survival curves
**[A]** TA patients (upper curve) demonstrated a tendency for longer survival than DC patients (lower curve). Five year survival: 62% for the TA group vs. 55% for the DC patients. However, the difference failed to reach statistical significance ($P > 0.05$). **[B]** Patients with early MDS from both patient groups (upper two curves) benefited from significantly longer survival than the patients with advanced MDS (lower two curves, $P = 0.009$). Although TA patients with both early (RA/RARS) and more advanced MDS survived longer than their respective early and advanced DC patients, these differences failed to reach statistical difference




DC = patients from Washington, DC, USA (1986–1987), TA = patients from Tel Aviv, Israel (1999–2009), MDS = myelodysplastic syndromes, RA/RARS = refractory anemia/refractory anemia with ring sideroblasts

subtypes indeed demonstrates a significantly longer survival for all early (RA/RARS) patients from both groups together, compared with the survival of more advanced FAB subtypes from both patient groups together (RAEB, RAEB-t, CMML, $P = 0.009$) [Table 3, Figure 1B]. However, no significant difference was recorded when TA patient survival was compared to DC patients, either in early or advanced FAB subtypes ($P > 0.05$). The 5YS for the FAB RA/RARS patients was 77% vs. 65%, for the TA and DC groups, respectively. For the more advanced FAB subgroups, the 5YS was 43% and 37% for the TA and DC patients, respectively. Again, none of these survival differences reached statistical significance.

## DISCUSSION

Significant progress has been made in MDS over the last 2 to 3 decades [1-4]. We have a better understanding of the disease biology and molecular genetics. We diagnose more patients, and identify them earlier than in the past because of greater awareness and modern techniques. We have introduced novel therapeutic approaches into clinical practice. These advances, as well as the investment of money and effort of many investigators along with the collaboration of patients, should have changed the disease picture. However, is the picture really different? Is the outcome better? This study represents a modest effort to answer these questions.

This type of analysis is limited by a relatively small number of patients and its retrospective nature. The two patient cohorts, with similar populations of typical urban areas in two Western countries and treated in tertiary referral medical centers, are not identical and differences in them might not be only temporal, but also geographic, social, ethnic, and demographic. The decades separating both groups have seen changes in additional factors such as in the medical systems, practice, and supportive care. These factors affect the analysis and the interpretation [8]. In addition, one should take into consideration that the DC group included all MDS patients from a registry, while the more recent TA cohort included only patients who eventually became transfusion-dependent. It should also be emphasized that despite the fact that the TA patient group represents a more recent period (1999–2009), the role of novel therapeutic agents, including immune-modulating and hypomethylating agents, was not analyzed in this study.

Nevertheless, despite these methodological limitations, several lessons can be learned, and cautious conclusions can be drawn. MDS patients from the TA group, compared with patients in the DC group, were older, perhaps reflecting the aging population in general. Patients in the TA group also tended to have more co-morbidities, especially cardiovascular diseases, which are common in an aging population. These TA patients had a lower MCV and lower levels of iron. This may be explained by the fact that they were older. The older TA patients might have had a greater likelihood to have iron deficiency [9] in addition to their MDS. This finding might be associated with a lower MCV. The TA patients also had fewer cytopenias and tended to be classified as having a more favorable MDS (i.e., RA/RARS according to FAB) or low-risk MDS according to IPSS. These results probably reflect the diagnosis being made in earlier stages of the disease.

The question of prognosis and survival of MDS patients over time remains open. On the one hand, TA patients were diagnosed earlier and had features of an earlier and more favorable disease. Based on this, one would expect an improved survival in this group. On the other hand, their older age and increased co-morbidities and transfusion dependence would lead one to expect a decrease in their survival, as seen, for example, in heart failure patients with anemia [10]. Since the data were taken from the time of diagnosis, the transfusion dependence at a later point in the disease was not an issue. However, the age and co-morbidities are influential, and likely balance the better prognostic factors. In the end, although there was a tendency toward minimal 5YS advantage in the TA patients compared to the DC patients (62% vs. 56%), this difference was not statistically significant. Further investigation with larger groups is required to determine the differences in prognosis and survival over time.

The prognosis of MDS patients in more recent decades compared with those of the past was recently investigated by Neukirchen and colleagues [8]. Using the Dusseldorf MDS registry, they analyzed the survival of 4147 patients diagnosed during the last 30 years. They found an improved survival in MDS patients diagnosed after 2002 (30 vs. 23 months), but this prolonged survival was restricted to high-risk MDS patients. These high-risk MDS patients diagnosed between 2002 and 2014 survived 19 months, while those diagnosed between 1982 and 2001 survived only 13 months. Interestingly, the prognosis of low-risk MDS patients remained about the same despite the 30 years of progress. In an attempt to sort out the reasons for the improved prognosis in high-risk MDS patients, the researchers suggested that a better supportive care might be responsible for the benefit, as well as the fact that these later patients received less aggressive chemotherapy. They also excluded the possibility that the improved prognosis among high-risk MDS patients could be related to early diagnosis, since improved prognosis could not be demonstrated in low-risk MDS patients. These findings are consistent with Fenaux and colleagues [11], who demonstrated a survival advantage with azacitidine in high-risk MDS patients. The Neukirchen analysis [8] is also consistent with our findings, if one takes into consideration that most of our patients were classified as low-risk MDS [8].

In the future, comparisons among patient cohorts should be greatly improved. Currently, there is much more information available for each patient with MDS. Not only are the mor-

phology of the bone marrow cells and the blast count used, but also the cytogenetics and molecular data. In addition, using this information allows for improved scores to make better comparisons among individuals and groups of patients. Finally, such data are collected and stored methodically in large MDS registries, as in the European EUMDS, for example. As such, with this additional information for each patient, comparisons among cohorts of different times and different locations would be much more meaningful.

### CONCLUSIONS

Despite the limitations of the study, which require cautious interpretation of the conclusions, we have found that, although MDS patients of the later time period were older and were diagnosed with more cardiovascular co-morbidities, they had fewer cytopenias and tended to have earlier disease, but a tendency toward greater but not significant survival. It is likely that novel agents, not included in this analysis, as well as a better understanding of the biology of the disease, will further improve the outcome in MDS.

**Acknowledgements**

Dr. Ofira Ben-Tal was instrumental in the design of this study. She passed away in 2014. This manuscript is dedicated to her memory.

**Correspondence**

**Dr. M. Mittelman**

Department of Medicine A, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel, **Fax:** (972-3) 697-4855, **email:** moshemt@tlvmc.gov.il

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**Capsule**

## Watching kidney cancer metabolism

Clear cell renal cell carcinoma (ccRCC) is the most common and aggressive form of kidney cancer and undergoes extensive metabolic reprogramming. **Courtney** and co-authors infused a glucose isotope into patients with primary ccRCC who were undergoing surgery and traced metabolic and isotopic flux. Compared with cells of the adjacent kidney, tumor cells exhibited prominent glycolysis, whereas the presence of tricarboxylic acid (TCA) cycle metabolites (indicating glucose oxidation) was diminished. ccRCC tumors were more glycolytic compared with brain and lung tumors from different patients. In one patient who was infused with an acetate isotope (acetate is a direct substrate of the TCA cycle), low TCA cycle turnover of metabolites was also observed. This phenomenon describes the Warburg effect of metabolism in ccRCC and highlights metabolic differences in different types of cancer.

*Cell Metab* 2018; 10.1016/j.cmet.2018.07.020

Eitan Israeli

**Capsule**

## Metastatic drivers same as primary

Treatment decisions for cancer patients are increasingly guided by analysis of the gene mutations that drive primary tumor growth. Relatively little is known about driver gene mutations in metastases, which cause most cancer-related deaths. **Reiter** and colleagues explored whether the growth of different metastatic lesions within an individual patient is fueled by the same or distinct gene mutations. In a study of 76 untreated metastases from 20 patients with different types of cancer, all metastases within a patient shared the same functional driver gene mutations. Thus, analysis of a single biopsy could help oncologists select the optimal therapy for patients with widespread metastatic disease.

*Science* 2018; 361: 1033

Eitan Israeli