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Original Article

Costs and quality of life in patients with myelodysplastic syndromes

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Abstract: Myelodysplastic syndromes (MDS) encompass a range of myeloid neoplasms characterised by a defect in haematopoietic stem cell maturation, resulting in peripheral cytopenias. As a major consequence, most MDS patients become anaemic, so as to require red blood cell transfusions. To investigate the costs and the impact on quality of life (QOL) of MDS-separately in transfusion-independent (TI) and -dependent (TD) patients-a literature search was conducted. From Medline and Embase, 742 studies were identified, of which 17 were considered eligible. Total medical costs per patient/year range from $ 9,840 to $ 19,811 for the TI condition and from $ 29,608 to $ 51,066 in the TD condition, more than doubling when moving from the former condition to the latter. With regard to QOL, in the transition from TI to TD, QOL could be reduced by half depending on the studies. The TD condition negatively impacts on costs and the QOL of patients with MDS. Therapeutic strategies that reduce transfusion dependence may lead to broad benefits for patients and the community.

Keywords: Myelodysplastic syndromes, anemia, transfusion dependence, quality of life, medical costs

Introduction

Myelodysplastic syndromes (MDS) are a varied group of haematopoietic neoplasms, characterised by defects in the proliferation, differentiation and maturation of bone marrow stem cells, with an increased risk of evolution to acute myeloid leukaemia (AML) [1], a progression which occurs in about 30% of patients with MDS [2].

Ineffective haematopoiesis occurs with dysplastic morphological alterations in one or more cell lines (white blood cells, red blood cells and platelets), peripheral blood cytopenias and progressive bone marrow failure [3]. Patients with MDS therefore tend to develop anaemia, neutropenia, thrombocytopenia or a combination of all three.

Until relatively recently, MDS received little attention by researchers, partly due to the difficulties in their epidemiological quantification, as they are present mainly in the geriatric population and are frequently misdiagnosed [4]. Only in 1999 MDS were firstly classified as neoplastic conditions by the WHO [5].

In 1997 a system was introduced for the prognostic evaluation of MDS, named IPSS (*International Prognostic Score System*), which defines life expectancy and the likelihood of transformation into AML in a prospective manner, based on three haematologic parameters: number of cytopenias, percentage of marrow blasts and karyotype [6].

The IPSS recognises 4 different categories of risk: low, intermediate-1, intermediate-2 and high, which are associated with an increasing likelihood of progression to AML and increasingly low survival (from approximately 72 months for low risk to 4 months for high risk). Another prognostic score index, named WPSS, includes transfusion-dependence as a prognostic parameter [7].

The most authoritative studies published to date suggest that the incidence of MDS in Europe and the USA is between 3 and 12 cases

every 100,000 inhabitants per year [8-15]. The differences observed in the various geographic areas can be attributed to three variables that differ amongst the various populations examined: environmental risk factors, mean age and diagnostic sensitivity/data capture capacity.

A common aspect to all studies is the relationship between increase in age and incidence of MDS. The study conducted by Germing et al., which analysed the data of the Dusseldorf Registry on 575,000 subjects collected between 1991 and 2001, shows that in the 60-70, 70-80 and 80-90 age brackets, incidence rises from 8.7 to 24.5 and 31.3 per 100,000 inhabitants, respectively [16]. This data suggests that MDS are more frequent than acute leukaemias, with an incidence that is very close to that of multiple myeloma and chronic lymphatic leukaemia [17].

The first therapeutic approach for MDS, still employed today, is supportive care, including transfusions, growth factors, antibiotics and iron-chelating agents, aimed at reducing the morbidity and mortality caused by cytopenias. New pharmacological products have recently been introduced, which can slow down the progression of the disease to AML and reduce the need for transfusions [18]. The lower need of transfusion has had a positive effect, not only on patient survival, but also for the health care system, by reducing the high costs of MDS treatment, which is based essentially on transfusions [19].

A study conducted on 467 patients for 10 years starting from the diagnosis of MDS highlighted the existence of a significant correlation between the need for transfusions and a reduction in overall survival or the time to progression to AML, suggesting a more severe underlying disease in patients with a higher transfusion intensity [7]. Frequent use of transfusions also has a negative impact on the quality of life (QOL) of patients, who experience chronic fatigue, are at risk of infection and are emotionally threatened by an uncertain future [20].

Although MDS have come to be recognised as an important oncologic condition little information is available on the costs of the disease and the consequences of repeated transfusions in terms of treatment costs and QOL for patients with MDS.

Given that 80% of patients with MDS are anaemic at diagnosis and more than 40% require regular red blood cell transfusions during their disease [21], a literature search was performed with the aim of evaluating the impact of transfusion dependence on the costs of MDS treatment and on QOL of patients. A patient is considered transfusion-dependent when he/she requires 2 or more red blood cell units over an 8-week period [22].

Materials and methods

A search was run on Medline and Embase using the key words: "*myelodysplastic syndromes*", "*quality of life*" and "*cost*". In order to restrict the research area without excluding pertinent publications, the key words were used as follows: a) publications containing the key word "*myelodysplastic syndromes*" only; b) publications containing "*myelodysplastic syndromes*" and "*quality of life*"; and c) publications containing "*myelodysplastic syndromes*" and "*cost*". Medline is the U.S. National Library of Medicine's® main reference database with 19 million publications (particularly in the biomedical field) in more than 5,600 international journals [23]. Embase is a biomedical and pharmacological database that includes Medline records plus five million other references not included in Medline [24].

The search was restricted to papers published in English between 2003 and 2012. We considered original research articles, reviews and papers published as abstracts, whereas work published as editorials, comments, case reports and news was excluded.

Given the breadth of the literature search, which was considered necessary in order to include all potentially pertinent studies, the combination of the key words chosen resulted in 742 publications. For the purpose of analysing the cost of treatment and the QOL of patients with transfusion-dependent (TD) or transfusion-independent (TI) MDS, we judged 17 publications to be relevant, of which 10 were published as articles and 7 as abstracts. The great quantity of material that was discarded is due, primarily, to the fact that they were of a primarily clinical nature or, even when present, content concerning QOL and costs was absolutely marginal.

Results

A report follows on the 17 selected publications.

An initial overview

With regard to cost analysis, the thorough literature review conducted by Brereton et al., [25] provided an estimate of the societal cost of intermediate-2 and high risk MDS in the United Kingdom. With an estimated incidence of 761 new patients each year, the overall cost range was put at between 12 and 16 million pounds (with a mean cost per patient of approximately £ 18,400). Much of these costs are dupe to hospitalisation (approximately 85% of the total) and transfusions; a relatively modest weight is attributed to loss or reduction in the work productivity of patients and their caregivers.

Instead of estimating the total societal cost of MDS, as presented in the previous publication [25], Greenberg et al., [26] only estimated the component associated with the pure costs of drugs for the treatment of MDS (in this case those at low and intermediate-1 risk) in the first year of treatment. To do so, the Authors devised a complex decision-making model based on: 1) the guidelines issued by NCCN (*National Comprehensive Cancer Network*) concerning the drugs recommended (Epoetin alfa, darbepoetin, filgrastim, azacitidine, decitabine, lenalidomide, antithymocyte globulin, cyclosporin A and the iron-chelating agents deferasirox and deferoxamine). for the treatment of cytopenia, doses and duration of treatment-all according to the risk and improvement target for the various symptomatic cytopenias; 2) the probability of response to first-, second- and third-line therapy obtained from a review of current literature; 3) the unit cost of the medications, calculated using the reimbursement lists applied by Medicare and Medicaid or other sources of insurance; 4) the estimated frequency of use for each medication, when they could be used alternatively. The mean annual cost of medicines for the treatment of cytopenias was estimated to be $ 63,577, of which 96% for the treatment of symptomatic anaemia. This estimate does not take into account the costs incurred for transfusions and the corresponding iron-chelating therapy. Based on the assumption that about 35% of all patients with MDS are transfusion-dependent, the authors estimated a further cost of $ 41,412 for this group.

Santini et al., [19] evaluated the societal cost of MDS in Italy. They used data collected through the COSMiQ (Societal costs of myelodysplastic syndromes and quality of life in Italy) study, based on a sample of patients treated at 7 Italian haematology centres (3 in Northern Italy, 2 in the centre of the country and 2 in the south). The analysis conducted on 225 patients (of which 88% at low and intermediate-1 risk), estimated an overall cost related to the consumption of healthcare and non healthcare resources and productivity loss for patients and caregivers of € 27,980 per patient/year. More than 98% of the total cost was borne by the National Health Service. The cost-drivers identified were anti-anaemia drugs in low- and intermediate 1-risk patients and anticancer agents in intermediate-2 and high-risk patients. Transfusion dependence proved to be a statistically significant predictor of cost increase ($P = 0.006$).

Once again, Santini et al., [27] analysed in one Italian transfusion centre, the distribution of the cost of a red blood cell transfusion, which the Authors calculated to be € 493. This figure refers to the direct components only and therefore does not include costs potentially associated to the transfusion, such as iron overload, transmission of infections and adverse events caused by immune mechanisms. The above amount, which is due primarily to personnel costs, breaks down into components connected with the donation (24% of the total), processing (47%) and transfusion (27%) of red blood cells, plus overheads (2%).

The study conducted in the US by Bozkaya et al., [28] shows that the cost of treating with lenalidomide transfusion-dependent patients with MDS with 5-q deletion (loss of part of the long arm of chromosome 5) is more than offset by the savings related to the fact that lenalidomide reduces transfusion dependence and, consequently, the associated complications.

A number of articles and abstracts have described the deterioration in QOL of patients with MDS.

The results of a study conducted by the Myelodysplastic Syndromes Foundation on

Table 1. Cost breakdown (mean per patient/year) [39]

Costs	€	%
By type of resource		
Outpatient services	4.950	33%
Hospital services	4.506	30%
Medications	5.427	37%
total	14.883	100%
By type of morbidity		
MDS	13.870	93%
Comorbidities	1.013	7%
total	14.883	100%

data from 29 patient forums in the US and Europe [29] showed fatigue to be the symptom that has the greatest effect on patients' QOL, although a fundamental role is also played by the time required to manage the disease (doctors' appointments, diagnostic tests, transfusions and management of adverse events). Similar conclusions were drawn by a study conducted by Twiss et al. [30]: on a sample of 23 transfusion-experienced patients, in addition to the restrictions imposed by the transfusion procedure in itself, the discomfort of iron-chelating therapy was also seen to be relevant. Schuler [31] reports that erythropoiesis-stimulating factors, such as erythropoietin and darbepoietin, allow a temporary improvement in the QOL of various subgroups of patient with MDS. With regards to the new hypomethylating agents and lenalidomide, the improvement in haemoglobin levels is associated with improvements in QOL that are not compromised by the side effects of these treatments [31-33].

Filloux et al. [34] investigated the potential predictive factors for use of transfusion, highlighting that transfusions are associated with a deterioration in QOL of patients with MDS and an increase in healthcare costs. The authors divided 205 French patients into high risk (IPSS ≥ 1.5) and low-risk (IPSS ≤ 1) groups and found the former to be characterised by a significantly higher frequency of use of transfusions than the latter (79% vs. 55%, $p = 0.006$).

The QLQ-C30 (Quality of Life Questionnaire-Core 30) was devised by the European Organization for Research and Treatment of Cancer (EORTC) as a multidimensional questionnaire (i.e. covering the various physical, emotive, social, etc. dimensions of the patient) to assess the quality of life a patient assigns to him/herself [35]. All the scores indicated by the patient are reported on a scale of 0-100 (an increasing quality scale) and can be aggregated with a single mean. By using the QLQ-C30 questionnaire on 32 Italian patients, Caocci et al. [36] revealed a significant ($p < 0.001$) difference between the QOL of non-transfused patients (66.7) and the QOL of transfused patients (32.9). There was a similar gap (65 vs. 31.8, respectively, $p < 0,001$) also for fatigue, in particular.

In addition to costs, the abovementioned COSMiQ study conducted by Santini et al. [19], also evaluated the QOL of MDS patients in Italy. The score (QLQ-C30) for overall health/QOL status was 65.1 and was significantly worse for transfusion-dependent patients ($p = 0.009$).

Pashos et al. [37] analysed the data obtained from a US registry based on a cohort of MDS patients treated with azacitidine. In particular, the analysis revealed that of the 85 patients who were TD at the start of treatment, 41 had become TI after 6 months; this change was associated with a significant improvement (i.e. of more than 7 points) in QOL, whereas QOL worsened for the 44 patients who remained TD.

In another large review (2678 articles identified, 46 eligible for inclusion), Platzbecker et al. [38] conclude that transfusion dependence is associated (in addition to reductions in survival and a higher comorbidity rate, as iron overload, immune reactions and infections)-with a higher economic burden and negative impact on QOL, despite the intermittent increase in haemoglobin levels achieved with the transfusions.

Healthcare resources and corresponding costs

The cost structure in TD patients (Germany): A retrospective study conducted by Kühne et al. [39] investigated the cost of MDS in low- and intermediate-1 risk TD patients in Germany, from the economic standpoint of the paying third party. The data was collected in seven specialist centres (six outpatient facilities and one university clinic), using online questionnaires completed by the GP using data from the patient's clinical records.

This made it possible to trace the use of hospitalisation, medication and red blood cell transfusions every quarter from 2001 to 2006. A

Table 2. Incidence of the cost of transfusions [39]

Product transfused:	No. of transfusions per patient/year	Cost per transfusion (€)	Total cost (€)
Red blood cells	17	161	2,737
Platelets	0.8	681	545
Cost of transfusions per patient/year			3,282
Cost of transfusions, as % of the total cost of MDS per patient/year (€ 14,883)			22%

total of 116 patients were enrolled (mean age 73 years, 41% males), for a total of 886 observation quarters (of which 776 in the six outpatient facilities). Mean follow-up was almost two years per patient.

By calculating the value (using price lists, formularies and expert opinions) of the healthcare resources used in the six facilities, the mean annual cost per patient was € 13,455 (data for 2007). In the university clinic, the figure was € 24.957. Overall, the mean annual cost per patient was € 14,883.

As the Authors assume the significant difference in cost between the two settings may be due primarily to administrative and billing differences, it was decided not to keep the analysis between the two types of health facility separated. The data was aggregated by obtaining the mean of the data for the two settings, weighted with the corresponding number of quarters observed (776 in the outpatient facilities and 110 in the university clinic). **Table 1** shows the cost breakdown-according to type of resource and morbidity-as identified for all the centres surveyed.

The same Authors also performed a cost analysis, for the six inpatient facilities only, dividing the caseload into patients with and without 5-q deletion. Since none of the differences in the various cost items was statistically significant, once again, no separate analysis was performed for the two types of patients.

The costs for medications show the highest incidence on the total (37%). In the six outpatient facilities, 52% of medication costs were for erythropoietin, 38% for iron-chelating agents and the remaining 10% for other medicinal products, in particular vitamins and immunosuppressants. More than two thirds of comorbidity-related costs (68%) were for hospital services and 31% for medication; whereas outpatient services accounted for the remaining 1%. No similar analysis was provided for the university clinic.

Based on the mean number of transfusions recorded per patient/year and the unit cost of transfusions (based on expert opinions), the Authors estimate that the cost for transfusions constitutes 22% of the total costs of MDS management (**Table 2**).

The impact of transfusion dependence on medical costs (United States): A retrospective study conducted by Frytak et al. [18] estimated the financial burden of MDS in the US for TI and TD patients separately. The source of the data was an administrative database of approximately 10 million insured subjects containing details of the various medical services utilised. The main criteria for selection from the database were age ≥ 55 years, the existence of at least two invoices with diagnosis of MDS (or one invoice plus evidence of transfusions) and absence of chemotherapy-induced anaemia in the 6 months prior to the observation start date (Diagnosis of MDS was based on the ICD-9-CM codes: 205.20, 208.20, 238.7, 284.9, 285.0). Three hundred and thirty six TD patients (defined as those with proof of ≥ 2 transfusions in 2 months, at least one week apart, and a third transfusion 3 to 6 months after the first) and 2,864 TI patients were identified. In this latter cohort, the mean age was 70 years, 47% were males and 10% of patients were newly-diagnosed-characteristics that are significantly different from those in the TD cohort (mean age 74 years, males 56%, new diagnosis 27%). The data was collected over a three-year period, between 2000 and 2003, with individual histories of at least 6 months subsequent to the start of observation. As an aside, the numerical disproportion between TD and TI patients could be partially attributed to the selection criteria for the former, which may have been particularly restrictive.

The costs of admissions (to hospital wards and Emergency Department visits), outpatient clinic and doctors' practice appointments, medication and transfusions were recorded. The overall mean annual cost (adjusted for demograph-

Table 3. Analysis of the "medical care" cost component [18]

Medical resources (mean data per patient)	TI patients	TD patients
Physical quantities (No. of units used per year)		
Hospitalisations	0.6	2.2
Emergency Department visits	0.8	2.4
Outpatient facility visits	7.8	28.4
Office visits	22.8	36.3
Costs (% of the total)		
Hospitalisations	49%	47%
Emergency Department visits	2%	2%
Outpatient facility visits	27%	32%
Office visits	22%	19%

Table 4. Transfusion cost analysis [18]

Facility used	No. of transfusions/patient/year	Cost/patient/year ($)
Inpatient hospital	1.2	8,522
Outpatient facility	9.6	7,521
Other*	0.8	543
Total	11.6	16,586

*For example: long-term hospitalisation, free-standing facility.

ic characteristics and comorbidities) was $ 19,811 (of which 85% for medical care and 15% for medication) for TI patients and $ 51,066 (92% for medical care and 8% for medication) for TD patients. Of this latter sum ($ 51,066), costs of $ 16,586 were due to transfusions (equal to half the difference in cost between TI and TD), whereas medication costs have a marginal effect on the total: 8%-15%.

Table 3 analyses the main component of the total costs for TI and TD patients, namely medical care, providing details of the healthcare resource items both in terms of the physical quantities used and their proportion of the total value.

A TD patient is admitted to hospital- or examined in outpatient facilities, such as transfusion centres or hospital outpatient centres- more than three times (2.2/0.6 = 3.6) a TI patient, goes to Emergency Department almost three times (2.9) as often and attends almost twice (1.6) as many office visits.

The other important cost item to be analysed is that concerning transfusions, the dependence on which has been recognised as the most important cost-driver. In the TI cohort, where just 10% of patients had had one or more transfusions during the study period, the mean number of transfusions per patient/year was 0.14, compared to 11.6 in the TD cohort.

It appears appropriate to highlight that transfusion-related costs were calculated on the basis of the specific cost of the transfusion incurred for the blood product (whole blood or red blood cell concentrate), administration of red blood cells, and corresponding analyses and/or counts. These exclude, for example, Emergency Department examinations for post-transfusion complications or reactions.

Table 4 provides an analysis of the mean transfusion costs incurred in 1 year for a TD patient. Most transfusions (9.6) are performed in outpatient facilities. The highest cost component concerns those few transfusions (1.2) performed on an inpatient basis. **Table 4** shows the stark difference between the mean cost of a transfusion on an inpatient ($ 7,102) and outpatient ($ 783) basis.

The predictors of cost increase of MDS (United States): Goldberg et al. [40] estimated the costs of newly-diagnosed MDS, high lighting those associated with transfusion dependence. Invoices for the health services used by insured subjects for the study period (from the beginning of 2003 to the end of 2005 or death) were extracted from Medicare's standard analytical files (SAF). Patients were identified with the following criteria: age ≥ 65 years, presence of the MDS code (ICD-9-CM: 238.7) on at least one invoice in the first quarter of 2003, no invoices with the same code in 2002 (in order to select newly-diagnosed patients only), no anaemia for known causes or myeloid leukaemia. This criterion was used to obtain a more uniform follow-up period for all patients, starting from the beginning. The services used included hospitalisation in inpatient wards, emergency department admissions, outpatient appointments and growth factor therapy.

In the database, the Authors identified 307 TI patients, defined as such when there are no

Table 5. Use (over a three-year period) of health resources [40]

Health resources	TI patients	TD patients
In physical terms		
Hospitalisations		
hospitalised patients: proportion of total	67%	91%
mean number of admissions per patient	1.8	3.7
mean length of stay (days)	4.7	7,2
Emergency department visits		
patients examined: proportion of total	74%	88%
mean number of appointments per patient	3.3	4.2
Hospital outpatient department visits		
patients examined: proportion of total	95%	98%
mean number of appointments per patient	19.7	29.7
Physician office visits		
proportion of patients examined	96%	96%
mean number of appointments per patient	35.6	42.3
Proportion of patients who received growth factor treatment	26%	59%
In terms of costs (% of the total)		
Hospitalisations	40%	44%
Outpatient department visits	10%	13%
Physician office visits	35%	30%
Other forms of care (Skilled Nursing Facility, Durable Medical Equipment, Home Health Agency, Hospice)	15%	13%

transfusion invoices in the database for the study period (mean age 77 years, 44% males), and 205 TD patients (mean age 78 years, 49% males). There were no significant differences between the two cohorts in terms of comorbidities at baseline.

During the three-year follow-up period, the use of healthcare resources was significantly lower for TI patients than TD patients. More specifically, TI patients were admitted to hospital in 67% of cases vs. 91% for TD patients; the mean duration of hospitalisation was 4.7 days for TI patients vs. 7.2 days for TD patients; and whereas just 26% of TI patients were treated with growth factors, the percentage rises to 60% for TD patients. An analysis of clinical outcomes also revealed a higher mortality rate and probability of progression to AML for transfused patients of 64% *vs.* 30% and 18% *vs.* 3.9%, respectively.

The greater consumption of healthcare resources by TD patients over the three-year observation period (2003-2005) is reflected by a mean cost of $ 88,824, about three times that estimated for TI patients ($ 29,519). In TD patients, the cost for transfusions amounted to $ 17,237, approximately 30% the incremental cost between the two cohorts.

In **Table 5**, all data concerning the use of healthcare resources in physical terms differs significantly ($p < 0.05$) between the two cohorts, with far greater use by T patients (the only exception-with nonsignificant differences-being the proportion of patients examined in outpatient facilities and office visits). For the T cohort, it is particularly interesting to note the proportion of patients treated with growth factors (more than double the other cohort), and of patients requiring hospital admission (almost one third more, almost two hospitalisations more per patient and 50% more days in hospital than the TI cohort).

In both cohorts, hospital admissions and physician's office visits together have a similar incidence-albeit with different weights-of three quarters of the total cost.

As regards inpatient admissions, that represent the most significant cost component, **Table 6** provides an interesting analysis of the causes of hospitalisation for the two cohorts.

The study eventually investigated the factors contributing to increase the mean total cost per patient, net of the cost for transfusions. To this end, the Authors used a multiple regression model in which the (logarithm off) the mean monthly cost of each patient was the dependent variable, whereas the demographic characteristics, baseline comorbidities, transfusion status (TI/TD) and any surgical complications

Table 6. Analysis of the causes of inpatient admissions [40]

Reasons for inpatient admission (main diagnosis)	NT patients		T patients	
	No. of admissions	%	No. of admissions	%
All causes	553	100%	758	100%
MDS	11	2%	55	7.3%
Diseases of the circulatory system	166	30%	188	24.8%
Congestive heart failure	42	7.3%	66	8.7%
Cancer	51	9.2%	111	14.6%
Acute myeloid leukaemia	0	0%	23	3%

Table 7. Impact of cost predictors [40]

Predictors	Percentage increase in cost
Dyspnoea	77%
Sepsis	72%
Arrhythmia	51%
Bacteraemia	49%
Transfusions	48%
Congestive heart failure	43%
History of heart problems	32%
Pneumonia	30%

constituted the explanatory variables (predictors). **Table 7** shows the proportional increase that the presence of each predictor brings to the mean monthly cost.

The presence of clinical complications is therefore predictive, to varying degrees, of increases in cost. Transfusion dependence is also an important cost-driver, having an impact on the mean basic monthly cost equal to a 48% increase in the same. It goes without say that if in the regression model the total costs also included the costs of red blood cell administration; the economic impact of transfusions would have been even higher. By concentrating on newly-diagnosed patients only, the Authors conclude that the analysis may underestimate the overall economic burden of MDS. Indeed, it is reasonable to suppose that the economic impact of the disease increases not only with progression, but also with an increase in mean age.

Quality of life

QOL in relation to transfusion dependence (United States, France, Germany and United Kingdom): A study conducted by Szende et al. [41] consisted in a sample estimate of the utility scores that can be attributed to three possible health statuses of a patients with MDS: TI reduced transfusion (RT) and TD. In health economics, the quality of life considered is that associated with being in a given condition of health. It can be analysed according to the many dimensions of everyday life (physical, social, psychological, etc.). The term "utility" refers to the subjective perception the patient has of his/her own QOL, summarised as a single numerical value. Based on literature and validated by an authoritative expert clinician, the descriptions of the three statuses indicated in the questionnaires administered to patients participating in the study refer to the various levels of severity/intensity of the problems that specific aspects of the condition cause to patients: reliance on transfusions and the healthcare provider; need to organise one's life around contacts with medical staff; fatigue and tiredness that interfere with normal exercise routines; the disease impact on social and family life; health-related concerns for the future; discomfort caused by the condition, its treatment and the feeling of being at risk of infection; reliance on others to look after oneself and perform everyday activities; the feeling of being a hindrance for the family; a feeling of unhappiness, hopelessness and helplessness.

Preferences were elicited by filling out the questionnaires during individual interviews, using the time trade-off (TTO) method on a scale of between 0 (death) and 1 (perfect health). The utility attributed to a given health situation can be measured using various methods, the most commonly used of which is the time trade-off method [42]. This is an iterative process in which a patient is asked to choose the better alternative between a longer life expectancy but in a condition of compromised health, and a shorter life expectancy in perfect health. The process is repeated until the patient deems the two proposals to be equally desirable. In short, the patient ultimately defines how many years of life (in current conditions) he/she would be willing to forego, out of the next ten, in order to enjoy a perfect health in the remaining years. The utility score the patient attributes to his/

Table 8. Predictors of QOL in MDS [32]

QOL indicators[1]	Predictors[2]	Effects[3]
QoL-E		
Physical wellbeing	Age (years)	–0.48
	Charlson's index (2-5 vs. 0-1)[4]	–14.2
	Haemoglobin (g/dL)[5]	+1.69
	Transfusions (Yes vs. No)[6]	–7.2
	Time from baseline (months)	–0.29
Functional wellbeing	Charlson's index (2-5 vs. 0-1)[4]	–15.5
	Haemoglobin (g/dL)[5]	+2.99
	Transfusions (Yes vs. No)[6]	–8.3
Social wellbeing	Charlson's index (2-5 vs. 0-1)[4]	–15.6
	Haemoglobin (g/dL)[5]	+2.15
	Transfusions (Yes vs. No)[6]	–6.7
	Marital status (married vs. *single*)	–9.8
	Time from *baseline* (months)	–0.42
Fatigue	Charlson's index (2-5 vs. 0-1)[4]	–8.6
	Haemoglobin (g/dL)[5]	+1.45
	Sex (male vs. female)	+3.3
Illness-related disorders	Charlson's index (2-5 vs. 0-1)[4]	–8.8
	Haemoglobin (g/dL)[5]	+1.53
	Transfusions (Yes vs. No)[6]	–6.8
	Time from *baseline* (months)	–0.38
EQ-5D	Charlson's index (2-5 vs. 0-1)[4]	–9.9
	Haemoglobin (g/dL)[5]	+1.77
	Transfusions (Yes vs. No)[6]	–4.4

[1]Measured on a scale of 0 (worst possible value) to 100 (best possible value). [2] Significant values only are shown ($p < 0.05$). [3]Estimated using multivariate analysis. They measure the (+) or (–) change in QOL corresponding to a 1-unit increase in predictor. [4]At baseline. Charlson's comorbidity index is a predictor of death at ten years in patients with comorbidities. Each disease is assigned a score (from 1 to 6, depending on the risk of mortality associated to it), which is then added to any others to obtain a single summarising score [45]. [5]At each visit. [6]In the three months preceding the visit.

her current health is obtained by subtracting from 1 (utility corresponding to perfect health), the proportion of forgone years of the total (i.e. the relative disutility perceived by the patient); for example, if the answer was 2 (years), utility would be 1-2/10 = 0.8. The patient therefore evaluated the three possible health statuses according to the respective descriptions. The EQ-5D questionnaire was also employed but only when collecting the descriptive statistics (socio-demographic and baseline clinical variables) of the sample. For some time, the EQ-5D (EuroQOL-5Dimensions) has been the instrument of election used in health economic studies. It is a two-part questionnaire. The first part reconstructs the subject's health profile according to 5 dimensions (mobility, looking after him/herself, anxiety or depression, daily activities, suffering or distress), each one with three severity levels. The respondent's answers are then weighted using the utility scores obtained with the TTO method for the general population and summarised through an algorithm with a value between 0 (the utility attributed to death) and 1 (the utility attributed to perfect health). In the second part of the questionnaire, the respondent is asked to indicate on a graduated scale from 0 to 100 (VAS, Visual Analogue Scale) the utility he/she attributes to his/her QOL [43].

A total of 47 MDS patients were interviewed (8 in the United States, 9 in France, 9 in Germany, 21 in the United Kingdom). In this sample, mean age was 67 years, 45% were males, and the mean time from diagnosis was 5 years. 87% of patients had had previous transfusions. Of these, 49% had received at least one transfusion in the previous three months. The mean EQ-5D score was 0.78.

In the end results, utility of the first health status (TI) had a value (0.84) that was significantly higher than that for RT (0.77) and TD (0.6).

These scores, which were measured by the TTO method directly on patients, reflect the utility patients attribute to their personal situation, unlike the generic instruments (such as the EQ-5D), used to reflect the utility scores of the general population. Regardless of which of the two is more appropriate for decision-making purposes, the results obtained show that patients with MDS attribute a great utility to transfusion independence, which suggests the importance of the new treatments, whose purpose is to achieve precisely this independence.

Factors associated with the QOL of patients with MDS (Italy): Oliva et al. [32] conducted a prospective, observational, multicentre study to investigate the factors with a major impact

Table 9. Cost data

Type of cost	Cost per patient/year		Country	Comment	Reference
	TI pat.	TD pat.			
Societal cost	£ 18,400		UK		Brereton et al., 2011 [25]
Societal cost	€ 27,980		I		Santini et al., 2011 [19]
Healthcare costs		€ 14,883	D	TD patients only	Kühne et al., 2010 [39]
Healthcare costs	$ 19,811	$ 51,066	USA		Frytak et al., 2099 [18]
Healthcare costs	$ 9,840	$ 29,608	USA	Annualised cost data	Goldberg et al., 2012 [40]
Drugs costs	$ 63,577	$ 104,989	USA	TI patients: anti-anaemia medication TD patients: anti-anaemia medication, iron-chelating agents and transfusions	Greenberg et al., 2008 [26]

Table 10. QOL data

Instrument	QOL		Country	Reference
	TI pat.	TD pat.		
QLQ-C30	66.7	32.9	I	Caocci et al., 2007 [36]
QLQ-C30	65.1		I	Santini et al., 2011 [19]
TTO	0.84	0.6	USA, F, D, UK	Szende et al., 2009 [41]
EQ-5D VAS	63	53	I	Oliva et al., 2012 [32]

on the QOL of patients with MDS. The study, which started in March 2007, involved 14 Italian centres, enrolling newly-diagnosed MDS patients with IPSS ≤ 2 and at least one cytopenia. Patients were subsequently evaluated at 1, 2, 3, 6, 12 and 18 months from enrolment. Patients with histories of other neoplastic conditions were excluded.

Of the 148 patients included in the study (mean age 72 years, males 56%), one in four (26%) was TD (defined as requiring at least 1 unit of transfusion a month for a period of at least 3 months).

QOL was evaluated using various instruments, in particular QoL-Ev.2 and EQ-5D (using a visual analog scale with the latter). The baseline values obtained with the EQ-5D were 63 in TI patients and 53 in TD patients, respectively (p = 0.004). QOL-Ev.2 is a specific questionnaire for MDS, comprising 28 items covering the various dimensions of QOL (including general, physical and functional and a disease-specific dimension, comprising 7 items). The scores the patient assigns to each item in each dimension are eventually standardised and aggregated as mean value of QOL (variable from 0 to 100) for the same dimension [45].

Generally speaking, QOL is not influenced by the passage of time. The only significant deterioration was recorded after 12 months from the start of the study in the QoL-E domain that specifically concerns MDS (-7.4, 95% CI -12.9 to -1.9, p = 0.0024).

In the study, various factors were seen to influence the QOL of patients with MDS (**Table 8**). Among such factors, the level of haemoglobin is the only one that has a positive correlation with QOL. The Authors also report a positive correlation between male gender and QOL for the "fatigue" item of QoL-E only.

All other predictors have a negative relationship with quality of life. The most important include multiple or severe comorbidities (Charlson's index > 1) and transfusion dependence, intended as the discomfort and inconvenience caused by the transfusion itself, rather than the anaemia condition in general. The multiple regression model used made it possible to separate the impact of transfusion dependence on QOL from the effect of statistical confusion generated by the association between transfusion dependence and haemoglobin level (in that the latter is usually lower in transfused patients).

Discussion

A study was conducted on costs and QOL in patients with MDS, dedicating a special attention to the differences between TI and TD status. A search run on Medline and Embase databases led to the identification of 742 reports, of which 17 were chosen for the analysis. This apparently restricted proportion is absolutely in line with those reported in other literature searches on the same subject [38, 46].

Concise data on the costs (**Table 9**) and quality of life (**Table 10**) obtained from the significant body of analytical information brought to light by the search, is provided below.

Considering the different settings in which the original studies were conducted, caution is required when making comparisons, which should be considered first and foremost a rough indication of the disease's economic impact and of the additional costs associated with transfusion dependence. Of the various publications considered, the estimate produced by Greenberg et al. [26] would appear to be particularly far off, in terms of magnitude, the estimates contained in the other publications presented in this study. In addition, the Authors [26] did not make any mention of this inconsistency in the discussion section of their article.

In any case, this research on MDS aims to explore the differences in cost and quality in relation to TI and TD status, rather than their absolute values. **Table 9** shows that, when passing from the former to the latter, healthcare costs more than double [18], or triple [40], and the costs of drugs go up by two thirds [26]. In particular, resource consumption analysis shows that TD patients are hospitalised more than 3 times as often as TI patients and attend almost twice as many office visits (**Table 3**). It is also necessary to consider, however, that the greater economic burden of TD patients as compared to TI patients is due not only to the transfusions themselves, but also to the fact that this condition is generally associated with a more severe MDS status and consequently related to a worse prognosis for patients.

As far as costs are concerned, it can be observed that, as regards those associated with MDS in Italy (for which the information available is somewhat scarce), the use of administrative or longitudinal clinical databases would allow a significant improvement of knowledge in this field. To this purpose, a number of issues should be preliminary resolved in terms of a more sensitive and specific identification of the patients selected for analysis (based, for example, on the type of medication prescribed or diagnosis at admission or laboratory tests required); the main issue would be to identify indicators that distinguish TI and TD patients (typically: transfusions, to be obtained, when not specified in the aforesaid databases, with links to other archives, for example general medicine records).

The estimates for QOL in patients with MDS provided herein are fairly consistent with one another, despite the different instruments of measurement used. As a means of comparison with the general population, we can consider that the utility score measured using EQ-5D in the British general population, in the same age bracket considered here, is 0.78 [47]. In the passage from TI to TD, the deterioration in QOL goes from 50% [36] to 15% [32].

This literature search clearly reveals that transfusion dependence, in addition to exposing subjects to a higher risk of infectious complications, also has a negative influence on QOL in patients with MDS and increases the costs of managing the disease.

Until just a few years ago, supportive care, primarily consisting in transfusions, represented the only treatment strategy for MDS. The management of MDS patients changed when new treatment options became available. As far as MDS with intermediate-2 or high IPSS risk are concerned, the results of a randomised phase 3 study have shown that, compared to conventional treatment, treatment with azacitidine is able to increase overall survival by more than 9 months and progression to acute myeloid leukaemia by about 6 months [48]. The results of this study also showed that treatment with azacitidine also significantly reduces transfusion dependence: of those patients who were TD at the start of the study, 45% of subjects treated with azacitidine became red blood cell transfusion independent, compared to 11.4% of those enrolled in the branch allocated conventional therapy ($p < 0,0001$). In another type of patients with MDS, TD patients with loss of part of the long arm of chromosome 5 (5q deletion), a significant reduction in transfusion requirements was observed when they were treated with the immunomodulator lenalidomide [33]. In the study, 51.6% of treated patients became TI for more than 26 weeks, compared to 5.9% of patients administered placebo ($p < 0.001$).

This literature search demonstrates that the use of new medications able to contain or reduce transfusion dependence could be a rational alternative for healthcare decision-makers at various levels. It's worthy to notice that these high-cost therapies were available and administered in the studies conducted from 2008 about the costs of transfusion-dependency, so their cost/benefit ratio has

been partially evaluated and may not be applicable to all countries. On the other hand, the assessment of the cost-effectiveness profile of the new therapies should be confirmed by complete economic evaluations studies.

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