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Guideline 6-13 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

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An assessment conducted in October 2019 indicated that Guideline 6-13 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

Guideline 6-13 is comprised of 5 sections. You can acess the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/53186

Section 1:	**Recommendations**
Section 2:	**Guideline – Recommendations and Key Evidence**
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GLOSSARY

Acronym	Definition
13 cRA	13 cis-Retinoic acid
ABS	Abstract
AE	Adverse effects
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AML	Acute myeloid leukemia
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATG	Anti-thymocyte globulin
AZA	Azacytidine
BM	Bone marrow
BSC	Best supportive care
CALGB	Cancer and leukemia group B
CCO	Cancer Care Ontario
CG	Control group
CI	Confidence interval
CMML	Chronic myelomonocytic leukemia
CR	Complete response
CsA	Cyclosporine
d(s)	day(s)
DA	Darbepoetin alpha
DAC	Decitabine
Del(5q)	Chromosome 5q deletion syndrome
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EHA	European Hematology Association
EORTC	European Organization for Research and Treatment of Cancer
EPO	Epoetin alpha or Erythropoietin
ER	Erythroid response
ESA	Erythropoiesis stimulating agents
ESMO	European Society of Medical Oncology
est.	Estimate
FAB classification	French-American-British classification
FACT-An	Functional assessment of Cancer Therapy – Anemia

Acronym	Definition
G-CSF	Granulocyte colony-stimulating factors
GDG(s)	Guideline Development Group(s)
GFM	Groupe Francophone des Myelodysplasies
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony-stimulating factors
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HB	Hemoglobin
HI	Hematologic improvement
hist.	Historical comparison
HMA	Hypomethylating agents
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplant
ICT	Iron chelation therapy
IG	Intervention group
IMiD	Immunomodulatory drugs
IMRAW	International MDS Risk Analysis Workshop
IPSS-R	International Prognostic Scoring System (revised)
IQR	Interquartile range
ITT	Intention-to-treat
IU	International units
IV	Intravenously
IWG	International Working Group
LEN	Lenalidomide
LFS	Leukemia-free survival
M-CSF	Macrophage colony-stimulating factors
MDS	Myelodysplastic syndrome
MDS-u	Myelodysplastic syndrome, unclassifiable
MER	Major erythroid response
mos	Months
MPD	Myeloproliferative disorders
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NPM1	Nucleophosmin
nr	Not reported
NS	Not significant

Acronym	Definition
observ.	Observational
OIR	Overall improvement rate
OMHLTC	Ontario Ministry of Health and Long-Term Care
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
p.o.	Orally
PBO	Placebo
PEBC	Program in Evidence-Based Care
PFS	Progression-free survival
PLT	Platelets
PNH	Paroxysmal nocturnal hemoglobinuria
PR	Partial remission/response
pRBC	Packed red blood cells
prosp.	Prospective
PS	Performance status
Pts	Patients
QoL	Quality of life
QUALMS -1	Quality of Life in Myelodysplasia Scale
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RAP	Report Approval Panel
RARS	Refractory anemia with ring sideroblasts
RBC –TI	Red blood cells transfusion-independent
RBC-TD	Red blood cells transfusion-dependent
RCMD	Refractory cytopenia with multiline age dysplasia
RCTs	Randomized controlled trials
RCUD	Refractory cytopenia with unilineage dysplasia
rEPO	Recombinant epoetin alfa
restrosp.	Retrospective
rHEPO	Recombinant erythropoietin
ROBINS-I	Risk of Bias tool for non-randomized trials
RR	Relative risk
SAGE	Standards and Guidelines Evidence Directory of Cancer Guidelines
SC	Subcutaneous
SCT	Stem cell transplant
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network

Acronym	Definition
SNPa	Single nucleotide polymorphism array
TD	Transfusion dependent
TFS	Transformation-free survival
Thal	Thalidomide
THPO	Thrombopoietin
TTP	Time to progression
vs.	Versus
WBC	White blood cells
WHO	World Health Organization
wk(s)	Week(s)
Yr(s)	Year(s)

Systemic therapy for the treatment of adult patients with lower-risk myelodysplastic syndromes

Section 1: Recommendations

This is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVES

To provide guidance for the management of lower-risk myelodysplastic syndromes (MDS) using systemic therapy. Therapies include, but are not limited to:

- Hematopoiesis growth factors (i.e., erythropoiesis-stimulating agents [ESA] such as erythropoietin [EPO], granulocyte colony-stimulating factors [G-CSF], romiplostim, and eltrombopag)
- Lenalidomide in deletion 5q (del[5q]) MDS
- Lenalidomide in non-del(5q) MDS
- Hypomethylating agents (5-azacytidine [AZA] and decitabine [DAC])
- Iron chelation therapy
- Immunosuppressive therapy (i.e., cyclosporine [CsA] and anti-thymocyte globulin [ATG])

TARGET POPULATION

Adult patients (age ≥18 years) with lower-risk MDS, (i.e., International Prognostic Scoring System [IPSS] risk score ≤1.0, and IPSS (revised) score ≤3.5)

INTENDED USERS

Clinicians involved in the care of patients with MDS: hematologists, medical oncologists, oncology nurses, and oncology pharmacists.

RECOMMENDATIONS

Recommendation 1: Hematopoiesis stimulating agents (ESA)

A. Erythropoietin (EPO)

The Working Group recommends EPO with or without G-CSF in symptomatic anemic patients with lower-risk MDS.

Subgroups of low-risk MDS patients for which treatment with EPO is particularly recommended are: patients with MDS without excess blasts, those who have lower endogenous EPO levels, and those who are not transfusion-dependent.

The Nordic score [1] is recommended to identify patients who are unlikely to respond.

B. G-CSF /macrophage colony-stimulating factors; romiplostim; eltrombopag

G-CSF: The Working Group members recommend the use of G-CSF in synergy with recombinant human erythropoietin in ESA non-responders.

The subgroups of patients for whom G-CSF are particularly recommended are those with ringed sideroblasts.

Romiplostim: The Working Group members do not recommend the use of romiplostim outside a clinical trial setting at this time.

Eltrombopag: The Working Group members do not recommend the routine use of eltrombopag outside a clinical trial setting at this time.

Qualifying Statements for Recommendation 1A

- The Nordic score [1] is useful at identifying patients who are unlikely to respond.
- Darbepoetin can be administered at a dose of 500 µg every two to three weeks; EPO can be given at a dose of 40,000-60,000 units weekly. A 12-week trial is recommended with dose escalation after a six-week trial in non-responders. For EPO, dose escalates from 40,000 units to 60,000 units weekly. For darbepoetin, escalate from 500 µg every three weeks, to every two weeks to every week. This dose escalation can occur along with the addition of G-CSF (see recommendation 1B below). Suggested target hemoglobin is 110 to 120 g/dL in transfusion-independent patients; in patients who are transfusion-dependent, the suggested goal of treatment is transfusion independence.

Qualifying Statements for Recommendation 1B

- Consider the use of G-CSF in synergy with recombinant erythropoietin after initial six to eight-week trial of EPO without adequate response.
- The dosing of G-CSF is flexible but should be given a minimum of two to three times/week and titrated to a white blood cell count of $<10\times10^9$/L.
- It is reasonable to consider eltrombopag for short-term use in patients with bleeding or prior to surgical intervention. The median daily dose to achieve a response is 50 mg (range, 50-175 mg) with a median time to response of two weeks (range, 1-15 weeks) and a median chansge in the platelet count of 124×10^9 /L (interquartile range 50-217×10^9/L).

Recommendation 2: Lenalidomide in del(5q)

A. For patients with lower-risk MDS who are transfusion-dependent with or without additional cytogenetic abnormalities that have failed an ESA or are not candidates for an ESA, the Working Group recommends lenalidomide.

B. The recommended lenalidomide dose and schedule is 10 mg a day on days 1 to 21 of a 28-day cycle for a minimum of 16 weeks

C. The Working Group members do not recommend the use of lenalidomide in combination with other agents outside a clinical trial.

D. Working Group members recommend using dose reductions to manage adverse events such as neutropenia and thrombocytopenia.

E. For patients who are not transfusion-dependent, the Working Group recommends a first-line watch and wait strategy or treatment with ESA first.

Qualifying Statements for Recommendation 2

Patients who have symptomatic anemia but who are not transfusion-dependent were considered by the consensus panel to be candidates for lenalidomide as well.

- Patients with >1% p53 nuclear protein expression may be at higher risk of acute myeloid leukemia transformation [2]; therefore, immunohistochemical screening is a potential option for this subpopulation to guide potential intensification of therapy.

Potential intensification could mean allo-transplant in younger patients, perhaps with novel interventions post transplant, clinical trials, hypomethylating agents, other clinical trials, and closer monitoring. At the present time, p53 testing (by immunohistochemistry) requires further validation. Thalidomide was not recommended alone or in combination for any IPSS risk by Leitch et al. because the adverse effects of thalidomide have been demonstrated to be high [3], and the Working Group members agree with this recommendation.

- No evidence is available at this point to recommend lenalidomide in combination with other agents in this population.

Recommendation 3: Lenalidomide in non-del(5q)

It is reasonable to consider lenalidomide as a line of treatment for transfusion-dependent patients with lower risk and non-del(5q) who are ineligible or refractory to ESA.

The recommended lenalidomide regimen is 10 mg/day orally on days 1-28 of a 28-day cycle for 16 weeks.

Qualifying Statements for Recommendation 3

- Patients previously treated with ESA and with lower monthly transfusion need (e.g., ≤2) are most likely to reach transfusion independence when treated with lenalidomide.
- In case of adverse events, use dose reductions (refer to Recommendation 2D).

Recommendation 4: Hypomethylating agents

AZA or DAC:

AZA or DAC can be offered as options to patients with lower-risk MDS without del(5q), with clinically significant cytopenia(s).

Qualifying Statements for Recommendation 4

- In existing guidelines, AZA is recommended for patients who have a high or intermediate-2 IPSS score [4], but it is generally not recommended as a first-line treatment for patient with lower risk.
- There may be a subgroup of patients with lower-risk MDS that are at a higher risk of progression. Patients without del(5q) who do not respond to EPO, and who may not be candidates for further intensive therapy, may benefit from treatment with AZA or DAC.
- The preferred dose and schedule for AZA is 75 mg/m^2 for five days of each 28-day cycle. The preferred dose and schedule for DAC is: 20 mg/m^2 per day subcutaneously for three consecutive days at the beginning of every 28-day cycle.

Recommendation 5: Immunosuppressive therapy (i.e., CsA and ATG)

Horse ATG in combination with oral CsA: CsA can be offered as an option to selected patients with lower-risk MDS who have failed or are ineligible for ESAs if anemic, or have clinically significant cytopenia(s).

Recommended regimen: ATG at a dose of 40 mg/kg/day should be given over 4 to 6 hr for four days. CsA should be started on day 14 at a dose of 5-12 mg/kg/day in two divided doses (every 12 hr) for 180 days with dose adjustments based on drug levels (target 200-400 ng/mL).

See qualifying statement below for adverse events.

Qualifying Statements for Recommendation 5

- The decision on which treatment option to use should involve a patient-centred discussion with a hematologist/medical oncologist. Patients should be aware of the higher risk of serious adverse events such as febrile transfusion reactions, and hepatic and hematologic adverse events with ATG and CsA.
- Patients who are more likely to benefit from immunosupressive treatment include: age <60 years, trisomy 8, recent transfusion dependence, paroxysmal nocturnal hemoglobinuria clones, HLA-DR15 serotype and hypocellular MDS. At the National Institute of Health, the three independent prognostic factors for response were age <60 years, HLA-DR15+, and treatment with ATG and CsA in combination.

Recommendation 6: Iron chelation therapy

It is reasonable to offer iron chelation to highly transfused patients with elevated ferritin (>1000 ng/mL) with lower-risk MDS.

Recommended regimen: the Working Group members recommend following recommendations for iron chelation therapy in hemoglobinopathies. The Working Group members prefer oral iron chelation over parenteral because it is more tolerable and compliance is significantly higher.

Qualifying Statement for Recommendation 6

- The dose and schedules used for MDS patients are based on those used for populations of patients with other hemoglobinopathies.

Recommendation 7: Other agents

The Working Group members do not recommend the use of ezatiostat, infliximab, amifostine, siltuximab, or topotecan outside a clinical trial setting.

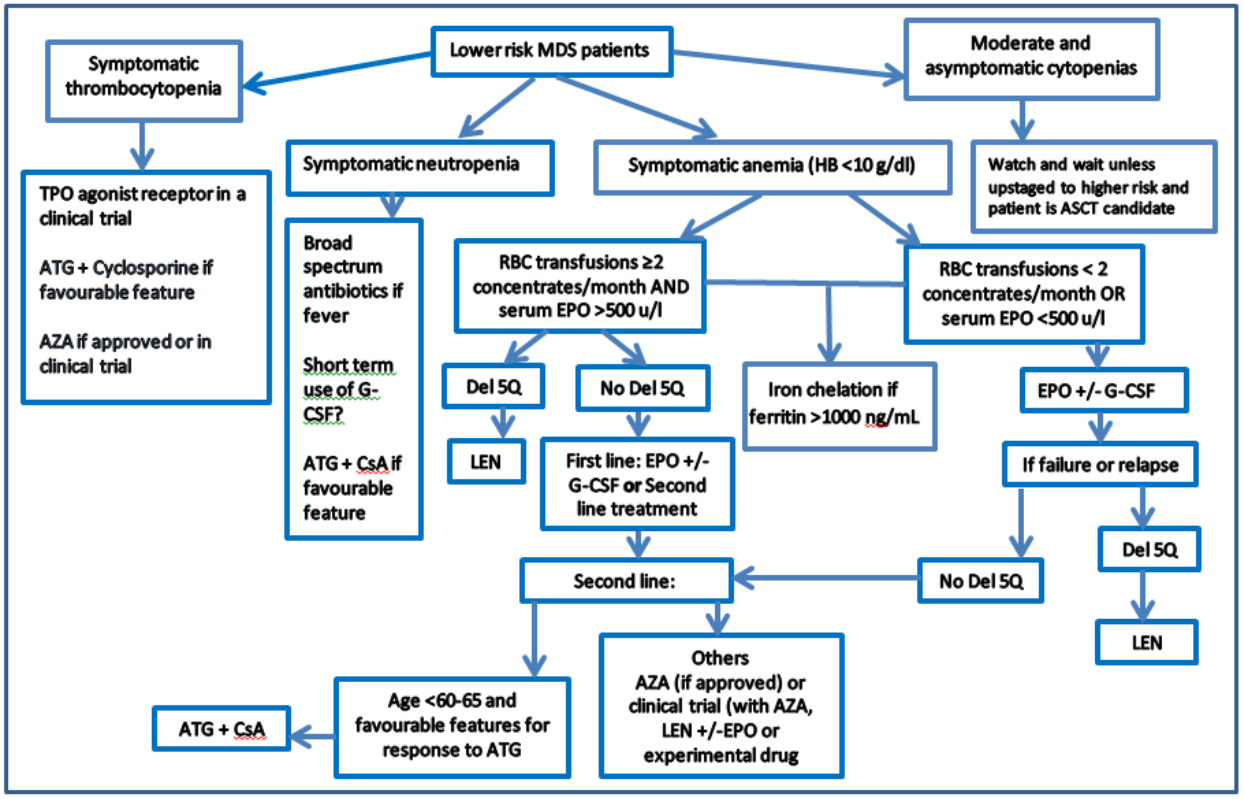

Figure 1-1. Treatment algorithm for the systemic treatment of lower risk myelodysplastic syndromes. Adapted from Figure 3 in: Fenaux P, et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3): iii57–iii69 doi:10.1093/annonc/mdu180, with permission of Oxford University Press on behalf of the European Society for Medical Oncology.