Evidence report for bone marrow transplant for myelodysplastic syndrome

Evidence Synthesis

Prepared by EBSCO Information Services

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Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. For each outcome, Evidence Synthesis Process tables will then articulate the method selected for evidence synthesis and justification of that method. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the Evidence Synthesis Process tables will be extended to include the method to produce noncomparative responses.

For summary statements representing a plain language summary of evidence appraisal and synthesis
We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

For summary statements representing a plain language summary of descriptive sources
Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of the references we consulted. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, we will provide this general parenthetical citation as part of the longer descriptive summary component that precedes the simplified summary statement.

Note: Although the scoped options are "allogeneic bone marrow transplant" and "no allogeneic bone marrow transplant" (the latter allowing any approach to therapy other than bone marrow/stem cell transplant), there are many terms for allogeneic bone marrow transplant (see the "Abbreviations" section in Scoping). Accordingly, we use many of these terms interchangeably in this evidence report, but we standardize on "bone marrow transplant" for evidence synthesis statements for ease of understanding.

Results – Summary of Findings

FAQ 1: What does the treatment involve?

Allogeneic bone marrow transplant (BMT)

For the transplant, bone marrow will be taken from someone who is at least partially matched to your genes. Your health care team will then give you this bone marrow through your vein. Before you have the transplant, you may take a medication like azacitidine or decitabine for something called “bridging”. This can help get your blood ready for transplant. It may also be used to help keep your myelodysplastic syndrome under control while waiting for a donor or while waiting for you to get healthy enough to have a transplant. Before you have the transplant, you will go through something called “conditioning”. This uses chemotherapy and sometimes radiation to help get your body ready for the transplant. You will also be put on medication that helps prevent something called “graft vs. host disease”. This is discussed in FAQ 4 “What are the side effects or risks?”.

After conditioning and your transplant, your immune system will be weak for many months. You may need to take extra steps to protect yourself from infection. This may include things like avoiding people who are sick, avoiding yard work or being too close to plants or flowers, and eating a special diet.

How long you might need to be in the hospital for a transplant can vary a lot. Some people may be able to do some or all of the transplant as an outpatient. Some people may need to be in the hospital for several weeks. You can discuss this more with your health care professional.

Recovering from a transplant takes time. In addition to your immune system being weak, it is also common for people to have low energy and feel like they do not have their normal strength. It may take up to a year for you to feel like you are back to your normal self. You may also need to take up to a year away from work, but this can vary. You can discuss this more with your health care professional.

No allogeneic bone marrow transplant (No BMT)

Treatment varies from person to person, but might include:

- getting medicine to help control how cells behave, like azacitidine or decitabine
- getting red blood cells or platelets
- getting medication to remove extra iron from your body
- getting medication to help your body make red blood cells or white blood cells

If you take azacitidine or decitabine, you will get it in your vein or under your skin. These medicines are often given once a day for 5 to 7 days every 4 to 6 weeks. You may be given a medicine for nausea before you take either of these medicines.

You and your health care professional can discuss which of these treatments might be right for you.

(Sources consulted for FAQ 1 for both options include ASCO 2018, DynaMed 2018 – 2020, Killick 2014, Leukemia and Lymphoma Society 2018, Leukemia and Lymphoma Society nd, Mayo Clinic 2019, NIH 2018, NIH 2020)

FAQ 2: Will it help me live longer?

Allogeneic bone marrow transplant (BMT) vs. No allogeneic bone marrow transplant (No BMT)

There is not enough research to know if people who get a bone marrow transplant live longer, shorter, or for the same amount of time as people who do not get a bone marrow transplant.

On average, people at medium risk may live about 2 to 4 years. Some people will live longer. Some people will live shorter.

On average, people at high risk may live about 1 to 2 years. Some people will live longer. Some people will live shorter.

On average, people at very high risk may live about 9 months. Some people will live longer. Some people will live shorter.

(Low certainty based on the combination of a lack of comparative data and inferences from 3 validation studies: Alessandrino 2008, Della Porta 2015, and Scheid 2017)

FAQ 3: Will I get cancer or have the problem come back?

Allogeneic bone marrow transplant (BMT)

Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.

Of 100 people at medium risk, 11 to 25 (11% to 25%) may have their myelodysplastic syndrome come back within 1 year, and 11 to 30 (11% to 30%) may have it come back within 2 years.

Of 100 people at high risk, 28 (28%) may have their myelodysplastic syndrome come back within 1 year, and 33 to 35 (33% to 35%) may have it come back within 2 years.

Of 100 people at very high risk, to 37 to 55 (37% to 55%) may have their myelodysplastic syndrome come back within 1 year, and 43 to 70 (43% to 70%) may have it come back within 2 years.

(Low certainty based on 2 validation studies: Alessandrino 2008, Scheid 2017)

No allogeneic bone marrow transplant (No BMT)

Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.

Of 100 people at medium risk, 5 to 12 (5% to 12%) may get leukemia within 1 year, and 12 to 22 (12% to 22%) may get leukemia within 2 years.

Of 100 people at high risk, 15 to 18 (15% to 18%) may get leukemia within 1 year, and 30 to 33 (30% to 33%) may get leukemia within 2 years.

Of 100 people at very high risk, 32 to 33 (32% to 33%) may get leukemia within 1 year, and 45 to 52 (45% to 52%) may get leukemia within 2 years.

(Low certainty based on 1 validation study: Della Porta 2015)

It is assumed, on average, that people who take azacitidine and decitabine get leukemia less often or later than people who do not take azacitidine and decitabine.

(Certainty not rated for this descriptive summary; based on Gurion 2010)

FAQ 4: What are the side effects or risks?

Allogeneic bone marrow transplant (BMT)

Conditioning before bone marrow transplant can cause things like nausea, vomiting, diarrhea, hair loss, and fatigue. It also has risks like infection, bleeding, or major organs not working like they should. You will also take medication to prevent something called “graft vs. host disease”. The medication will increase your risk for infection and may have other side effects or risks depending on the specific medication used. You and your health care professional can talk about this more.

“Graft vs. host disease” is a risk after bone marrow transplant. It can be “acute” or “chronic”. It happens when the new cells from the bone marrow transplant get confused. This makes them attack parts of the body because they think those parts do not belong. Acute graft vs. host disease involves the skin, intestines, and liver. It can cause symptoms like a painful or itchy red rash, nausea, vomiting, and diarrhea. In bad cases, it can make someone dangerously sick. Chronic graft versus host disease can also involve the skin, intestines, and liver. It can involve other body parts as well, like the eyes, lungs, joints, and genitals. It can cause symptoms like thickened skin, changes in the color of the skin, dry eyes, cataracts, mouth ulcers, difficulty swallowing, weight loss, nausea, vomiting, diarrhea, shortness of breath, cough, muscle and joint pain, and dry, itchy, or burning genitals. In bad cases, people may be disabled by the symptoms.

Of 100 people treated with bone marrow transplant, within 100 days:

- 9 to 11 (9% to 11%) may die from issues related to the bone marrow transplant
- 38 (38%) may have acute graft vs. host disease

Of 100 people treated with bone marrow transplant, at 1 year:

- 44 (44%) may have acute graft vs. host disease
- 37 to 39 (37% to 39%) may have chronic graft vs. host disease

(Quantitative estimates have Moderate certainty based on 1 registry study: Atallah 2019; certainty not rated for other statements, which are descriptive in nature and have references listed in FAQ 1)

No allogeneic bone marrow transplant (No BMT)

If myelodysplastic syndrome is not treated or is not treated enough, it can cause low levels of red blood cells, white blood cells, and platelets. This can lead to things like fatigue, shortness of breath, infection, and bleeding. There are treatments to help keep red blood cells, white blood cells, and platelets as normal as possible, but these treatments have different side effects and risks. For azacitidine and decitabine, risks may include your blood cell numbers being too low or too high, your blood pressure dropping too low, infection, and fluid buildup in your lungs or stomach. Some people get infection with low white blood cells (these are the blood cells that fight infection). Side effects are common with these medicines. Side effects may include things like chest pain, nausea, vomiting, diarrhea, constipation, stomach pain, loss of appetite, fatigue, muscle or joint pain, dizziness, headache, trouble sleeping, and pain or redness where the medicine is given. You may have other side effects. Your health care professional can talk with you about which treatments you might need and the side effects and risks that might come with those treatments.

(See FAQ 1 for references; additional sources consulted include FDA 2020)

Search Summary

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	32	2
2nd-round (Systematic review searches)	25	0
3rd-round (Original article searches)	215	8
4th-round (Citation tracing)	1	1
Total	*273*	*11*

* Number shown is after deduplication

	Articles selected for evaluation (Author Year)
Systematic reviews	0
Randomized, controlled trials	0*
Other article types	11 (Alessandrino 2008, Atallah 2019, Greenberg 2012, Della Porta 2015, Nazha 2016, Neukirchen 2014,† Malcovati 2007, Malcovati 2011, Scheid 2017, Schetelig 2019,‡ Voso 2013)

*During our searches, we discovered a study design, rationale, and methods for a biologic assignment trial for (reduced-intensity) allogeneic bone marrow/stem cell transplant vs. best supportive care for patients 50 to 75 years of age: Blood and Marrow Transplant Clinical Trials Network #1102. The expected completion date is listed as December 2021; no results are available yet.

†Addressed in Critical Appraisal in the summary for Voso 2013

‡ Addressed in Critical Appraisal in the summary for Atallah 2019

Results – Synthesis Details

FAQ 1: What does the treatment involve?

In general, therapies in myelodysplastic syndrome can be grouped into two large categories: “curative” and “non-curative”. “Non-curative” therapies are often referred to as “supportive” or “best supportive care”, and can include a number of therapies, as discussed in the section below titled “No allogeneic bone marrow transplant (No BMT)”. At present, the only therapy considered to be (potentially) “curative” is allogeneic hematopoietic stem cell/bone marrow transplant (alloHSCT), with “curative” signaling that alloHSCT conceivably “removes” or otherwise directly addresses the underlying problem. However, one could debate the meaning of “curative” here, as patients can still have relapse/recurrence after alloHSCT, and current evidence does not permit clear inference into how alloHSCT might influence patient-relevant outcomes. This may be reflected in some major guidelines referring to alloHSCT as “potentially curative” rather than “curative” (European Society for Medical Oncology 2014). Nevertheless, major guidelines agree that alloHSCT should be considered as a first-line therapy in patients with higher-risk myelodysplastic syndrome if they are eligible to receive it based on health status and donor availability (European Society for Medical Oncology 2014, National Comprehensive Cancer Network 2020). However, the choice can still be considered preference sensitive if one considers the issues with the existing evidence as well as the inconvenience and risks associated with alloHSCT.

Allogeneic bone marrow transplant (BMT)

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

In allogeneic bone marrow transplant, hematopoietic (blood-forming) stem cells are removed from a healthy donor and given to the patient intravenously (this is the “transplant”). The donor is either a relative or an unrelated donor who is sufficiently genetically similar to the patient. Some patients may take a hypomethylating agent like azacitidine or decitabine before getting the transplant, possibly to help reduce the quantity of marrow blasts or as a temporizing therapy while identifying a donor or waiting for the patient’s health to (hopefully) improve to a state where s/he becomes eligible for transplant. This approach to therapy is called “bridging”. Regardless of whether a patient receives bridging, before the transplant occurs, s/he will undergo something called “conditioning”. Conditioning involves giving chemotherapy and sometimes radiotherapy to: eliminate or substantially decrease disease burden (i.e., the number of unhealthy cells), weaken the immune system to prevent the patient’s body from rejecting the transplanted cells, and help with something called “engraftment” (the transplanted cells reaching the bone marrow and beginning hematopoiesis). Conditioning can be myeloablative (standard intensity) or nonmyeloablative (reduced intensity). Prophylaxis against graft vs. host disease is also standard of care. Although there is no consensus on the regimen to use, there are common regimens (e.g., cyclosporine and methotrexate), and the central idea is immunosuppression. An institution must have a prophylaxis guideline in place to be acknowledged by accrediting organizations. Even with prophylaxis, however, graft vs. host disease is fairly common (see FAQ 4).

After transplantation, a patient will need close follow-up with the health care team for monitoring. Additionally, because of the conditioning that occurs prior to transplantation, patients will be immunocompromised, and as noted above, the medications used to help prevent graft vs. host disease also have immunosuppressive properties. It can take up to 6 months or longer for cell counts and the immune system to recover. Accordingly, during this time – and especially in the early phases of recovery – patients may be advised to take additional precautions to reduce the likelihood of infection

while their immune system recovers. These precautions may include things like avoiding contact with people who have any type of infectious illness (including simple infections like the common cold) or only having contact with such people with additional precautions (such as people wearing masks if someone has a common cold); not doing yardwork or otherwise handling or being too near to plants or flowers (given they are a potential source of microorganisms); exercising caution with pets (e.g., no rough play to avoid the potential for bites or scratches and having someone else change litter boxes for cats); and adhering to a low-microbial diet (e.g., avoiding raw or undercooked meat, fish, or eggs; raw honey; unwashed raw vegetables or fruit; or non-pasteurized dairy products).

While patients are in the hospital, they may be given parenteral nutrition until they can tolerate oral intake. Once they can tolerate oral intake, they may be advised to adhere to the above-noted low-microbial diet. Once their immune system has recovered, they may still be encouraged to see a dietician and/or follow certain dietary recommendations to ensure they are receiving a well-balanced diet with the hope of maximizing recovery.

The amount of time a person has to be in the hospital can vary considerably depending on his/her clinical characteristics, the intended treatment course, and the norms of the institution where s/he is receiving treatment. In some cases, all or part of the transplant can be done on an outpatient basis; in other cases, patients are admitted to the hospital, and the stay could last several weeks.

Recovering from a transplant takes time. In addition to the discussion above about immune system recovery, it often takes substantial time for people to regain their strength and energy. It is not uncommon for people to need up to a year to feel normal. People may need to take considerable time away from work, possibly up to a year for some people (though this depends on many factors, including the type of work a person does).

Although the above presents general information concerning what someone might expect, as with all considerations like this, patients will receive advice more specific to their situation from their health care team.

Descriptive Summary Results

For the transplant, bone marrow will be taken from someone who is at least partially matched to your genes. Your health care team will then give you this bone marrow through your vein. Before you have the transplant, you may take a medication like azacitidine or decitabine for something called “bridging”. This can help get your blood ready for transplant. It may also be used to help keep your myelodysplastic syndrome under control while waiting for a donor or while waiting for you to get healthy enough to have a transplant. Before you have the transplant, you will go through something called “conditioning”. This uses chemotherapy and sometimes radiation to help get your body ready for the transplant. You will also be put on medication that helps prevent something called “graft vs. host disease”. This is discussed in FAQ 4 “What are the side effects or risks?”.

After conditioning and your transplant, your immune system will be weak for many months. You may need to take extra steps to protect yourself from infection. This may include things like avoiding people who are sick, avoiding yard work or being too close to plants or flowers, and eating a special diet.

How long you might need to be in the hospital for a transplant can vary a lot. Some people may be able to do some or all of the transplant as an outpatient. Some people may need to be in the hospital for several weeks. You can discuss this more with your health care professional.

Recovering from a transplant takes time. In addition to your immune system being weak, it is also common for people to have low energy and feel like they do not have their normal strength. It may take up to a year for you to feel like you are back to your normal self. You may also need to take up to a year away from work, but this can vary. You can discuss this more with your health care professional.

No allogeneic bone marrow transplant (No BMT)

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

There are a number of treatments that do not involve bone marrow transplantation, such as transfusions (with red blood cell transfusions possibly being coupled with iron chelation depending on patient specifics), growth factors (e.g., erythropoietic therapy, granulocyte colony stimulating factor), and hypomethylating agents (azacitidine, decitabine). Which treatments might be warranted for a given patient depend on the patient's specific circumstances. Given (1) the common use or consideration of azacitidine or decitabine for patients with higher-risk myelodysplastic syndrome who are ineligible for or opt not to pursue bone marrow transplantation and (2) the more generic mechanisms of action of the other therapies listed here, we describe azacitidine and decitabine in additional detail.

Azacitidine and decitabine are both hypomethylating agents, meaning they cause hypomethylation of DNA. This may help restore normal gene expression and cell differentiation and proliferation while exerting cytotoxic effects for abnormal hematopoietic cells in the bone marrow. It is assumed, on average, that patients who receive treatment with these agents get leukemia less often or later than patients who do not receive these agents (e.g., Gurion 2010). Administration of either of these agents may be preceded by premedication with an antiemetic. It might be given intravenously or subcutaneously, though for decitabine, intravenous is considered the more established method for administration (subcutaneous dosing is considered off-label and not considered further here). Azacitidine is given daily for 7 days and repeated at 4-week intervals. Decitabine can be given in a 3-day or 5-day regimen that is repeated at 6-week intervals: in the 3-day regimen, decitabine is given over a 3-hour period every 8 hours for 3 days; in the 5-day regimen, decitabine is given over a 1-hour period every day for 5 days.

Descriptive Summary Results

Treatment varies from person to person, but might include:

- **getting medicine to help control how cells behave, like azacitidine or decitabine**
- **getting red blood cells or platelets**
- **getting medication to remove extra iron from your body**
- **getting medication to help your body make red blood cells or white blood cells**

If you take azacitidine or decitabine, you will get it in your vein or under your skin. These medicines are often given once a day for 5 to 7 days every 4 to 6 weeks. You may be given a medicine for nausea before you take either of these medicines.

You and your health care professional can discuss which of these treatments might be right for you.

(ASCO 2018, DynaMed 2018 – 2020, Killick 2014, Leukemia and Lymphoma Society 2018, Leukemia and Lymphoma Society nd, Mayo Clinic 2019, NIH 2018, NIH 2020)

FAQ 2: Will it help me live longer?

Unfortunately, comparative evidence for HSCT vs. other therapies is lacking. This is perhaps captured well by a 2018 systematic review (Bell 2018), who noted a general "lack of clinical evidence regarding effective treatments" for patients with high-risk myelodysplastic syndrome being a key impetus for their systematic review. After their review, they noted comparative statements are impeded by "a high degree of variability across study populations and specific subgroups, including age, number of previous therapy lines received, and distribution across IPSS risk categories". Indeed, as we note below, there is substantial concern for selection bias in the available evidence if one attempts to make comparative statements. Bell 2018 note an example of this in the discussion of their results, noting HSCT is performed "only in a fraction of potential patients" and that the median age of patients receiving HSCT was 52 to 60 years compared to a median age of 68 to 74 years for patients receiving hypomethylating agents/azacitidine.

We pre-specified reporting efficacy outcomes (FAQ2 and FAQ3) for HSCT treated patients and HSCT untreated patients expected according to their baseline risk category on either of the two most commonly used prognostic scoring systems (ie, IPSS-R or WPSS). Because we found multiple validation studies of these two systems, we first report the operational criteria we used for selecting the most robust validation study of each (separately for HSCT treated and HSCT untreated patients). We then report evidence tables with expected outcomes according to baseline risk, based on the results of the selected validation studies.

Operational criteria

Our first-round searching yielded the validation studies Malcovati 2007 and Greenberg 2012, both of which we summarized. Our subsequent searching of MEDLINE®/PubMed® identified multiple validation studies of the IPSS-R and WPSS prognostic scoring systems through our searches. We reviewed them in detail to determine advantages and drawbacks of each and to define criteria for selecting the most robust validation study(-ies) for both the IPSS-R and WPSS in both patients who did not receive a bone marrow/stem cell transplant (in whom these instruments were originally derived) and in subsequent validation studies in patients who did receive bone marrow/stem cell transplant.

In selecting validation studies to summarize, we set representativeness as our primary criterion. Operationally, we defined representativeness as preferring studies that were large and generalizable, ideally those based on a large database that combined multiple databases from multiple institutions from multiple countries. If no combined studies were available and there was >1 potentially eligible single country/single center validation study, we selected the largest and most representative study. As a secondary criterion, we assessed whether studies reported both survival and recurrence/progression outcomes on the prognostic scoring system being validated (and ideally on the other prognostic risk measure as well). However, if a study reported on both outcomes but did not fulfill our primary criterion of representativeness, this was not sufficient cause for it to be selected (as it could introduce risk of selection bias). Ultimately, our secondary criterion did not result in exclusion of any studies.

The reason(s) for selecting validation studies in addition to Malcovati 2007 and Greenberg 2012 are summarized below:

HSCT untreated patients

Della Porta 2015 was selected for summary because it is a validation study of the WPSS ('new' version) using a large database that combined multiple MDS patient databases and reported survival and progression. It also reported results that validate IPSS-R. It therefore represents the largest and most representative study that had a primary intent of validating the 'new' WPSS (though also providing data that validate the IPSS-R).

We also selected for summary Malcovati 2007. This is the initial validation study of the WPSS ('initial' version). The main difference between the 'initial' and 'new' version of WPSS is that in the 'initial' version of WPSS, the severity of anemia was defined by transfusion dependency, and in the 'new' version of WPSS, it is defined based on hemoglobin thresholds.

Because the 'new' version WPSS has been incorporated into evidence-based guidelines but the initial version is also still used, we considered summaries appropriate for both.

Voso 2013 was selected for summary because it is the largest and most representative study identified that had a primary intent of validating the IPSS-R (though it also reported results that validate WPSS).

HSCT treated patients

Alessandrino 2008 was selected for summary for WPSS, as it was the larger and more representative of two validation studies found.

Scheid 2017 was selected for summary for IPSS-R as it was the largest and most representative validation study identified.

Note:

- In many cases, estimates were obtained from inspection of published survival curves. See Critical Appraisal for details.
- In many cases, confidence intervals were not available. Where confidence intervals were reported, we include them.
- The "total sample size" listed in table headers represents the overall sample size for the respective validation cohort. The percentage of patients in each risk category is listed within the table. For instance, in Della Porta 2015, 19% of patients (1,128/5,326) were classified as WPSS Intermediate.
- Detailed descriptions of the variables comprising each prognostic scoring system and the strata within each system are available in Critical Appraisal
- Certainty for all estimates is Low due to low certainty regarding calibration with uncertainty in precision and accuracy for risk prediction. See Critical Appraisal for details.

Patients not treated with HSCT

WPSS prognostic risk category and median overall survival (Della Porta 2015, total sample size = 5,326)

	Intermediate	High	Very high
Percentage of patients in category	19%	24%	8%
Overall median survival, months	44	21	9

IPSS-R prognostic risk category and median overall survival (Della Porta 2015, total sample size = 5,326)

	Intermediate	High	Very high
Percentage of patients in category	21%	13%	11%
Overall median survival, months	35	20	9

IPSS-R prognostic risk category and median overall survival (Greenberg 2012, total sample size = 200)

	Intermediate	High	Very high
Percentage of patients in category	18%	14%	8%
Overall median survival, months	40.8	14.4	7.2

WPSS prognostic risk category and median overall survival (Malcovati 2007, total sample size = 739)

	Intermediate	High	Very high
Percentage of patients in category	23%	33%	12%
Overall median survival, months	48	26	9

IPSS-R prognostic risk category and median overall survival (Voso 2013, total sample size = 380)

	Intermediate	High	Very high
Percentage of patients in category	18%	7%	4%
Overall median survival, months (95% CI)	37.7 (31.4 to 62)	18.4 (12.6 to 52.6)	14 (6.4 to not reached)

WPSS prognostic risk category and median months survival (Voso 2013, total sample size = 380)

	Intermediate	High	Very high
Percentage of patients in category	17%	17%	4%
Overall median survival, months (95% CI)	46.6 (30.4 to 59.7)	33.1 (23.9 to 97.8)	14 (6.4 to not reached)

Patients treated with HSCT

WPSS prognostic risk category and median overall survival (Alessandrino 2008, total sample size = 238)

	Intermediate	High	Very high
Percentage of patients in category	18%	57%	13%
Overall median survival since transplant, months	not reached	12	9

IPSS-R prognostic risk category and median overall survival (Scheid 2017, total sample size = 579)

	Intermediate	High	Very high
Percentage of patients in category	24.4%	25.4%	21.1%
Overall median survival since transplant, months	20	12.5	8

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Overall survival	**Statement of insufficient evidence to make comparative statements** In addition to lacking data from randomized, controlled trials, the available observational evidence also comes from different, non-contemporaneous patient cohorts, and there is extremely serious concern for the potential of selection bias (the most prominent concern among other possible sources of bias or indirectness) to lead to misleading conclusions if one were to attempt to make comparative statements. Accordingly, we conclude the currently available evidence is insufficient to permit any comparative statements concerning treatment of MDS with HSCT vs. pursuing non-HSCT treatments.	**There is not enough research to know if people who get a bone marrow/stem cell transplant live longer, shorter, or for the same amount of time as people who do not get a bone marrow/stem cell transplant.**	***Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.*** ***Non-HSCT treatment*** **Use results from most representative validation study** We describe above the operational criteria we developed to select the most representative validation studies for the IPSS-R and WPSS. Among the studies selected as a result of executing these operational criteria, Della Porta 2015 emerged as being the most representative, providing validation of both the IPSS-R and WPSS (it is the largest study by far and included multiple sites internationally). Consideration of the other validation studies also suggested consistent estimates (especially considering the greater imprecision these much smaller studies have). Therefore, our conclusions are based on Della Porta 2015. ***HSCT treatment*** **Use results from most representative validation studies** We describe above the operational criteria we developed to select the most representative validation studies for the IPSS-R and WPSS. On execution of these operational criteria, 2 studies provided the most representative validation studies: Alessandrino 2008 for WPSS and Scheid 2017 for IPSS-R. Our conclusions are based on these studies.	**See "Evidence Synthesis Results" below.**

Comparison of bone marrow transplant to no bone marrow transplant

There is not enough research to know if people who get a bone marrow transplant live longer, shorter, or for the same amount of time as people who do not get a bone marrow transplant.

Prognostic estimates for patients not treated with bone marrow transplant

Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.

If risk stratifying by WPSS:

People at medium risk may live a little less than 4 years on average. Some people will live longer, and some people will live shorter.
People at high risk may live a little less than 2 years on average. Some people will live longer, and some people will live shorter.
People at very high risk may live about 9 months on average. Some people will live longer, and some people will live shorter.

If risk stratifying by IPSS-R:

People at medium risk may live a little less than 3 years on average. Some people will live longer, and some people will live shorter.
People at high risk may live a little less than 2 years on average. Some people will live longer, and some people will live shorter.
People at very high risk may live about 9 months on average. Some people will live longer, and some people will live shorter.

If combining the WPSS and IPSS-R (even though these risk strata are not necessarily the same):

People at medium risk may live about 3 to 4 years on average. Some people will live longer, and some people will live shorter.
People at high risk may live a little less than 2 years on average. Some people will live longer, and some people will live shorter.
People at very high risk may live about 9 months on average. Some people will live longer, and some people will live shorter.

(Low certainty based on 1 validation study: Della Porta 2015)

Prognostic estimates for patients treated with bone marrow transplant

Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.

If risk stratifying by WPSS:

People at high risk may live about 1 year on average. Some people will live longer, and some people will live shorter.
People at very high risk may live about 9 months on average. Some people will live longer, and some people will live shorter.
(Statement about intermediate/"medium" risk precluded by median survival not being reached in Alessandrino 2008 for this risk group, but given the very comparable outcomes between Alessandrino 2008 and Scheid 2017 for the high and very high risk categories despite using different prognostic risk models, one might infer with Very low certainty that the median survival for WPSS intermediate might have been fairly comparable to IPSS-R intermediate had Alessandrino 2008 had a larger sample size or longer duration of follow-up.)

(Low certainty based on 1 validation study: Alessandrino 2008)

If risk stratifying by IPSS-R:

People at medium risk may live a little less than 2 years on average. Some people will live longer, and some people will live shorter.
People at high risk may live about 1 year on average. Some people will live longer, and some people will live shorter.
People at very high risk may live about 8 months on average. Some people will live longer, and some people will live shorter.

(Low certainty based on 1 validation study: Scheid 2017)

If combining the WPSS and IPSS-R (even though these risk strata are not necessarily the same):

People at medium risk may live a little less than 2 years on average. Some people will live longer, and some people will live shorter.
People at high risk may live about 1 year on average. Some people will live longer, and some people will live shorter.
People at very high risk may live about 9 months on average. Some people will live longer, and some people will live shorter.

(Low certainty based on 2 validation studies: Alessandrino 2008, Scheid 2017)

Adjustments for use in a side-by-side decision aid

Although the risk classifiers (WPSS, IPSS-R) discriminate between the strata of intermediate, high, and very high risk, the actual risk in each stratum has low certainty (low calibration). A simplification to combine the option-specific results for each risk stratum (e.g., for the high-risk stratum, about 1 year with bone marrow transplant and a little less than 2 years with no bone marrow transplant, thus becoming about 1 to 2 years for both options) may be reasonable given there is no evidence to support differences between the options. There is also no evidence to support equivalence between the options, so that will be stated as well.

There is not enough research to know if people who get a bone marrow transplant live longer, shorter, or for the same amount of time as people who do not get a bone marrow transplant.

On average, people at medium risk may live about 2 to 4 years. Some people will live longer. Some people will live shorter.
On average, people at high risk may live about 1 to 2 years. Some people will live longer. Some people will live shorter.
On average, people at very high risk may live about 9 months. Some people will live longer. Some people will live shorter.

(Low certainty based on the combination of a lack of comparative data and inferences from 3 validation studies: Alessandrino 2008, Della Porta 2015, and Scheid 2017)

FAQ 3: Will I get cancer or have the problem come back?

See 'Operational criteria for study selection' under FAQ2, which also applies to FAQ3.

Evidence Review Tables

Note:

- In many cases, estimates were obtained from inspection of published survival curves. See Critical Appraisal for details.
- In many cases, confidence intervals were not available. Where confidence intervals were reported, we include them.
- The "total sample size" listed in table headers represents the overall sample size for the respective validation cohort. The percentage of patients in each risk category is listed within the table. For instance, in Della Porta 2015, 19% of patients (1,128/5,326) were classified as WPSS Intermediate.
- Certainty for all estimates is Low due to low certainty regarding calibration with uncertainty in precision and accuracy for risk prediction. See Critical Appraisal for details.

Patients not treated with HSCT – outcome of interest is leukemic transformation

WPSS prognostic risk category and proportion with leukemic transformation (Della Porta 2015, total sample size = 5,326)

	Intermediate	High	Very high
Percentage of patients in category	19%	24%	8%
Leukemic transformation (%)			
at 1 year	5%	18%	32%
at 2 years	12%	33%	52%

IPSS-R prognostic risk category and proportion with leukemic transformation (Della Porta 2015, total sample size = 5,326)

	Intermediate	High	Very high
Percentage of patients in category	21%	13%	11%
Leukemic transformation (%)			
at 1 year	12%	15%	33%
at 2 years	22%	30%	45%

IPSS-R prognostic risk category and transformation to acute myeloid leukemia (Greenberg 2012, total sample size = 200)

	Intermediate	High	Very high
Percentage of patients in category	18%	14%	8%
Median years for 25% of MDS patients to develop AML*	2.4	0.8	0.6

*This was the only outcome reported related to leukemic transformation in the validation cohort (no survival curves were published)

WPSS prognostic risk category and proportion with leukemic transformation (Malcovati 2007, total sample size = 739)

	Intermediate	High	Very high
Percentage of patients in category	23%	33%	12%
Leukemic transformation (%)			
1 year	12%	32%	64%
2 years	21%	38%	80%
5 years	33%	54%	84%

IPSS-R prognostic risk category and proportion with leukemic transformation (Voso 2013, total sample size = 380)

	Intermediate	High	Very high
Percentage of patients in category	18%	7%	4%
Leukemic transformation			
at 1 year	15%	43%	50%
at 2 years	35%	72%	100%

WPSS prognostic risk category and proportion with leukemic transformation (Voso 2013, total sample size = 380)

	Intermediate	High	Very high
Percentage of patients in category	17%	17%	4%
Leukemic transformation			
at 1 year	10%	31%	53%
at 2 years	34%	48%	78%

Patients treated with HSCT – outcome of interest is probability of relapse

WPSS prognostic risk category and probability of relapse (Alessandrino 2008, total sample size = 238)

	Intermediate	High	Very high
Percentage of patients in category	18%	57%	13%
Relapse probability			
at 1 year	11%	28%	55%
at 2 years	11%	35%	70%

IPSS-R prognostic risk category and probability of relapse (Scheid 2017, total sample size = 579)

	Intermediate	High	Very high
Percentage of patients in category	24.4%	25.4%	21.1%
Probability of relapse			
at 1 year	25%	27.5%	37%
at 2 years	30%	33%	43%

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Non-HSCT treated: % with leukemic transformation HSCT-treated: % with relapse	**Not applicable** In addition to lacking data from randomized, controlled trials and the available observational evidence coming from different, non-contemporaneous patient cohorts (leading to an extremely serious concern for selection bias), the outcomes defined for the different options are fundamentally different and thus non-comparable	**Does not apply**	***Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.*** ***Non-HSCT treatment*** **Use results from most representative validation study** We describe above the operational criteria we developed to select the most representative validation studies for the IPSS-R and WPSS. Among the studies selected as a result of executing these operational criteria, Della Porta 2015 emerged as clearly being the most representative, providing validation of both the IPSS-R and WPSS (it is the largest study by far and included multiple sites internationally). Consideration of the other validation studies also suggested consistent estimates (especially considering the greater imprecision these much smaller studies have). Therefore, our conclusions are based on Della Porta 2015. ***HSCT treatment*** **Use results from most representative validation studies** We describe above the operational criteria we developed to select the most representative validation studies for the IPSS-R and WPSS. On execution of these operational criteria, 2 studies provided the most representative validation studies: Alessandrino 2008 for WPSS and Scheid 2017 for IPSS-R. Our conclusions are based on these studies.	**See bolded synthesis statements below**

Comparison of bone marrow transplant to no bone marrow transplant

Does not apply (outcomes assessed for the respective options are different, namely leukemic transformation for the option of treatment without bone marrow transplant and recurrence of myelodysplastic syndrome for the option of treatment with bone marrow transplant)

Prognostic estimates for patients not treated with bone marrow transplant

Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.

If risk stratifying by WPSS:

Of 100 people at medium risk, 5 (5%) may get leukemia within 1 year, and 12 (12%) may get leukemia within 2 years.
Of 100 people at high risk, 18 (18%) may get leukemia within 1 year, and 33 (33%) may get leukemia within 2 years.
Of 100 people at very high risk, 32 (32%) may get leukemia within 1 year, and 52 (52%) may get leukemia within 2 years.

If risk stratifying by IPSS-R:

Of 100 people at medium risk, 12 (12%) may get leukemia within 1 year, and 22 (22%) may get leukemia within 2 years.
Of 100 people at high risk, 15 (15%) may get leukemia within 1 year, and 30 (30%) may get leukemia within 2 years.
Of 100 people at very high risk, 33 (33%) may get leukemia within 1 year, and 45 (45%) may get leukemia within 2 years.

If combining the WPSS and IPSS-R (even though these risk strata are not necessarily the same):

Of 100 people at medium risk, 5 to 12 (5% to 12%) may get leukemia within 1 year, and 12 to 22 (12% to 22%) may get leukemia within 2 years.
Of 100 people at high risk, 15 to 18 (15% to 18%) may get leukemia within 1 year, and 30 to 33 (30% to 33%) may get leukemia within 2 years.
Of 100 people at very high risk, 32 to 33 (32% to 33%) may get leukemia within 1 year, and 45 to 52 (45% to 52%) may get leukemia within 2 years.

(Low certainty based on 1 validation study: Della Porta 2015)

In line with our description of azacitidine and decitabine in FAQ 1 (What does the treatment involve?), we also note it would be reasonable to state it is assumed, on average, that patients receiving azacitidine and decitabine get leukemia less often or later than patients who do not receive azacitidine and decitabine (e.g., Gurion 2010). However, full appraisal and synthesis of this literature is beyond the scope of this evidence report.

It is assumed, on average, that people who take azacitidine and decitabine get leukemia less often or later than people who do not take azacitidine and decitabine.

(Certainty not rated for this descriptive summary; based on Gurion 2010)

Prognostic estimates for patients treated with bone marrow transplant

Note: The statements below are option-specific, but importantly, they are strictly prognostic for the group in question. Option-specific estimates cannot and should not be compared between options; their validity and meaningfulness are limited to within-option comparisons for prognostic inference.

If risk stratifying by WPSS:

Of 100 people at medium risk, 11 (11%) may have their myelodysplastic syndrome come back within 1 or 2 years.
Of 100 people at high risk, 28 (28%) may have their myelodysplastic syndrome come back within 1 year, and 35 (35%) may have it come back within 2 years.
Of 100 people at very high risk, 55 (55%) may have their myelodysplastic syndrome come back within 1 year, and 70 (70%) may have it come back within 2 years.

(Low certainty based on 1 validation study: Alessandrino 2008)

If risk stratifying by IPSS-R:

Of 100 people at medium risk, 25 (25%) may have their myelodysplastic syndrome come back within 1 year, and 30 (30%) may have it come back within 2 years.
Of 100 people at high risk, 28 (28%) may have their myelodysplastic syndrome come back within 1 year, and 33 (33%) may have it come back within 2 years.
Of 100 people at very high risk, 37 (37%) may have their myelodysplastic syndrome come back within 1 year, and 43 (43%) may have it come back within 2 years.

(Low certainty based on 1 validation study: Scheid 2017)

If combining the WPSS and IPSS-R (even though these risk strata are not necessarily the same):

Of 100 people at medium risk, 11 to 25 (11% to 25%) may have their myelodysplastic syndrome come back within 1 year, and 11 to 30 (11% to 30%) may have it come back within 2 years.
Of 100 people at high risk, 28 (28%) may have their myelodysplastic syndrome come back within 1 year, and 33 to 35 (33% to 35%) may have it come back within 2 years.
Of 100 people at very high risk, to 37 to 55 (37% to 55%) may have their myelodysplastic syndrome come back within 1 year, and 43 to 70 (43% to 70%) may have it come back within 2 years.

(Low certainty based on 2 validation studies: Alessandrino 2008, Scheid 2017)

Adjustments for use in a side-by-side decision aid

Does not apply; as discussed above, the outcomes are different

FAQ 4: What are the side effects or risks?

Allogeneic bone marrow transplant (BMT)

Akin to our approach for FAQs 2 and 3, we developed operational criteria to select the most representative study(-ies) reporting on the risks specified in Scoping (graft vs. host disease and mortality attributable to treatment). Specifically, we limited to studies with ≥400 participants and gave preference to studies with methods likely to yield the most representative data (all other things being equal/comparable, multisite studies were preferred to studies from a single institution, and more current data were preferred to less current data). Where applicable, we also culled records based on studies examining/utilizing the same database at different timepoints or for different research questions. This process yielded two studies informing risks: Atallah 2019 and Schetelig 2019. Schetelig 2019 was primarily informative for understanding the results of Atallah 2019, but it is not carried forward to Evidence Synthesis (details are in Critical Appraisal for the summary of Atallah 2019). Thus, our operational criteria for selection yielded Atallah 2019 as the single source for estimating risks associated with HSCT.

Evidence Review Table

Probability of acute and chronic graft vs. host disease and non-relapse mortality in patients treated with HSCT (Atallah 2019)

Outcome	% (95% CI) of outcome among people ≥65 years of age (n = 688)	% (95% CI) of outcome among people 55 to 64 years of age (n = 592)
Grade II-IV acute graft vs. host disease		
at 100 days	38 (34 to 42)	38 (34 to 42)
at 1 year	44 (40 to 48)	44 (40 to 48)
Chronic graft vs. host disease		
at 6 months	20 (17 to 23)	21 (18 to 25)
at 1 year	37 (33 to 40)	39 (35 to 43)
Non-relapse mortality		
at 100 days	11 (9 to 13)	9 (7 to 11)

Certainty for all estimates is Moderate. The evidence was downgraded for indirectness because it did not restrict to the prognostic risk categories for our scoped population of interest. Although about 52% of patients were classified as IPSS-R intermediate, high, or very high, about 22% were classified as IPSS-R low or very low and about 26% had missing IPSS-R. It is not clear to what extent the inclusion of patients classified as IPSS-R low or very low and patients with missing IPSS-R might have affected the univariate estimates. We consider non-relapse mortality at 100 days to be attributable to the transplant (see Critical Appraisal for details).

Evidence Synthesis Process

Approach taken and justification: option-specific measure	Results: option-specific measure
Use results from single study We describe above the operational criteria we developed to select the most representative study for scoped risks associated with HSCT. On execution of these operational criteria, 1 study provided the most representative data. Our conclusions are based on this study.	**See bolded synthesis statements below**

Descriptive Summary and Evidence Synthesis Results

As noted in FAQ 1, prior to receiving a bone marrow transplant, a person undergoes "conditioning" with chemotherapy and sometimes radiation. This can cause various side effects (e.g., nausea, vomiting, diarrhea, hair loss, mouth sores, ulcers, fatigue) and is not without risks (e.g., infection, bleeding, and – in severe cases – organ failure).

After a bone marrow transplant, the new immune system cells sometimes get confused and think parts of a person's body do not belong. When this happens, the immune system cells start to attack those parts of the person's body like they are an infection or cancer. This is called "graft vs. host disease", and there is an "acute" type and a "chronic" type. Graft vs. host disease can be mild, moderate, or severe. In the worst case, it can put a person's life at risk, particularly in the acute variant, and people with the chronic type can be disabled if their symptoms are severe. As noted in FAQ 1, patients are given prophylaxis to reduce this risk, but even with prophylaxis, graft vs. host disease is fairly common. Additionally, the prophylaxis for graft vs. host disease increases the risk for infections, among other agent-specific side effects and toxicities (e.g., methotrexate and hepatotoxicity).

Conditioning before bone marrow transplant can cause things like nausea, vomiting, diarrhea, hair loss, and fatigue. It also has risks like infection, bleeding, or major organs not working like they should. You will also take medication to prevent something called "graft vs. host disease". The medication will increase your risk for infection and may have other side effects or risks depending on the specific medication used. You and your health care professional can talk about this more.

"Graft vs. host disease" is a risk after bone marrow transplant. It can be "acute" or "chronic". It happens when the new cells from the bone marrow transplant get confused. This makes them attack parts of the body because they think those parts do not belong. Acute graft vs. host disease involves the skin, intestines, and liver. It can cause symptoms like a painful or itchy red rash, nausea, vomiting, and diarrhea. In bad cases, it can make someone dangerously sick. Chronic graft versus host disease can also involve the skin, intestines, and liver. It can involve other body parts as well, like the eyes, lungs, joints, and genitals. It can cause symptoms like thickened skin, changes in the color of the skin, dry eyes, cataracts, mouth ulcers, difficulty swallowing, weight loss, nausea, vomiting, diarrhea, shortness of breath, cough, muscle and joint pain, and dry, itchy, or burning genitals. In bad cases, people may be disabled by the symptoms.

Of 100 people treated with bone marrow transplant, within 100 days:

- **9 to 11 (9% to 11%) may die from issues related to the bone marrow transplant**
- **38 (38%) may have acute graft vs. host disease**

Of 100 people treated with bone marrow transplant, at 1 year:

- **44 (44%) may have acute graft vs. host disease**
- **37 to 39 (37% to 39%) may have chronic graft vs. host disease**
-

(Quantitative estimates have Moderate certainty based on 1 registry study: Atallah 2019; certainty not rated for other statements, which are descriptive in nature and have references listed in FAQ 1)

No allogeneic bone marrow transplant (No BMT)

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Because MDS can result in cytopenias across all 3 cell lines, the consequences of untreated or undertreated MDS are linked to the main functions of the 3 cell lines: anemia (red blood cells), infection (white blood cells), and bleeding (platelets).

As noted in FAQ 1, there are a number of treatments that do not involve bone marrow transplantation. As such, it is not practical to provide a description of all possible risks here. Rather, this can be addressed at the bedside by the clinician based on which therapies a given patient may be eligible for or receive. However, akin to our approach to FAQ 1, because the hypomethylating agents azacitidine and decitabine are commonly used or considered in this case, we include descriptions of serious risks and common side effects associated with these medications. The lists below are from the monographs for these two agents; adverse events included below occurred in ≥5% of participants at a rate ≥4% more than the control group (no comparative analyses were reported). Unfortunately, these agents have numerous adverse effects, which is perhaps unsurprising given their mechanism of action.

azacitidine*

risks may include:

- cytopenias, including febrile neutropenia
- infection (e.g., pneumonia, cellulitis)
- hypotension

side effects may include:

- chest pain
- redness, irritation, or pain at the injection site
- nausea, vomiting, abdominal pain, anorexia, constipation, diarrhea
- arthralgia, myalgia
- ecchymosis
- dizziness
- headache
- anxiety
- insomnia
- stomatitis
- gingival bleeding, other bleeding in the mouth
- fatigue
- dyspnea
- upper respiratory infection
- fever
- xerosis, rash

decitabine†

risks may include:

- cytopenias, including febrile neutropenia
- thrombocythemia
- pulmonary edema
- ascites
- infection (e.g., pneumonia, cellulitis)

side effects may include:

- blurry vision
- nausea, vomiting, reflux, abdominal pain, anorexia, constipation, diarrhea
- redness, irritation, or pain at the injection site
- hemorrhoids
- stomatitis
- tongue ulcers, glossodynia
- arthralgia, myalgia
- chest pain
- dysphagia
- fever
- peripheral edema
- rigors/chills
- fatigue
- pain or tenderness at unspecified site
- headache
- dizziness
- hypoesthesia
- insomnia
- confusional state
- urinary frequency
- upper respiratory infection
- rash, redness, or itching of skin
- alopecia
- ecchymosis

*The monograph includes a section describing "serious" events that occurred in "<5%" (≥5% was threshold for considering something a "Most Frequently Observed" adverse reaction) without tabulated details or an indication of frequency in the control group. This includes various adverse events, ranging from dehydration, neck pain, and loin pain to systemic inflammatory response syndrome, anaphylactic shock, and cerebral hemorrhage. However, the lack of detail about this list of adverse events ultimately renders the information largely unhelpful, so it is not included here.

†Various changes in blood tests (e.g., albumin levels, blood urea nitrogen levels) are not included here. The monograph also includes a list of "serious" events that occurred in an unreported portion of patients without tabulated details or an indication of frequency in the control group. This includes various adverse events, ranging from post-procedural pain and chest pain to mental status changes and cholecystitis to "pulmonary mass" and cardiopulmonary arrest. However, the lack of detail about this list of adverse events ultimately renders this information largely unhelpful, so it is not included here.

Because the intent of capturing these risks and side effects is not to help people choose between azacitidine and decitabine, but rather to give people an idea of what risks and side effects might be associated with these agents in general (as hypomethylating agents), in our bolded statement below, we seek to capture risks and representative/common side effects between the two medications.

Descriptive Summary Results

If myelodysplastic syndrome is not treated or is not treated enough, it can cause low levels of red blood cells, white blood cells, and platelets. This can lead to things like fatigue, shortness of breath, infection, and bleeding. There are treatments to help keep red blood cells, white blood cells, and platelets as normal as possible, but these treatments have different side effects and risks. For azacitidine and decitabine, risks may include your blood cell numbers being too low or too high, your blood pressure dropping too low, infection, and fluid buildup in your lungs or stomach. Some people get infection with low white blood cells (these are the blood cells that fight infection). Side effects are common with these medicines. Side effects may include things like chest pain, nausea, vomiting, diarrhea, constipation, stomach pain, loss of appetite, fatigue, muscle or joint pain, dizziness, headache, trouble sleeping, and pain or redness where the medicine is given. You may have other side effects. Your health care professional can talk with you about which treatments you might need and the side effects and risks that might come with those treatments.

(See FAQ 1 for references; additional sources consulted include FDA 2020)