Immunosuppressive treatment (IST) annual follow-up

Guide to the completion of the EBMT data collection form: IST_FU_annual_v1.0

21 August 2023

EBMT Registry
EBMT Clinical Research & Registry Department
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Immunosuppressive treatment annual/unscheduled follow-up

The IST annual/unscheduled follow-up form must be submitted to the EBMT Registry database annually after an IST episode or at time of patient death, whichever occurs first.

1. Date of follow-up:

Report the follow-up date which is the closest to the annual follow-up assessment post-IST. If the patient died or was lost to follow-up, enter the date the patient was last seen alive.

2. Survival status:

Indicate if the patient is last known to be Alive or Dead. If the patient is lost to follow-up, tick the box for Lost to follow-up.

3. Date of the last IST for this patient:

Report the start date of the immunosuppressive treatment episode that this follow-up is reported for.

Best response

4. Best response after this IST:

Report the best response achieved since the immunosuppressive treatment, even if the patient got worse again afterwards. The definitions of the best responses for severe aplastic anaemia can be found in Table 1. For congenital bone marrow failures, no formal response criteria are available.

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe aplastic anaemia</td>
<td>Not meeting any of the response criteria defined below</td>
</tr>
<tr>
<td>Stable disease/no change/no response</td>
<td>Not meeting criteria of partial or complete response</td>
</tr>
<tr>
<td>Complete Remission (CR)</td>
<td>All of the following:</td>
</tr>
<tr>
<td></td>
<td>- No evidence of clonal evolution, by marrow cytogenetic and flow cytometry</td>
</tr>
<tr>
<td></td>
<td>- Peripheral blood counts: hemoglobin &gt;10 gr/dL, absolute neutrophils &gt;1.0 x 10⁹/L, platelets &gt;100 x 10⁹/L</td>
</tr>
<tr>
<td></td>
<td>All of the following:</td>
</tr>
<tr>
<td></td>
<td>- haemoglobin normal for age</td>
</tr>
<tr>
<td></td>
<td>- neutrophils &gt;= 1.5 x 10⁹/L</td>
</tr>
<tr>
<td></td>
<td>- platelets &gt;= 150 x 10⁹/L</td>
</tr>
</tbody>
</table>
Table 1, definitions of best responses

| Partial Remission (PR) | All of the following: No longer meeting criteria for diagnosis of SAA  
Transfusion independence (defined as no need of any PRBC or platelet transfusion)  
Peripheral blood counts: hemoglobin >8 gr/dL, absolute neutrophils >0.5 x 10⁹/L, platelets >20 x 10⁹/L | At least one of the following:  
• transfusion independence (if previously required) doubling or normalization of at least one cell line  
• increase above baseline* by: 3 g/dl hemoglobin and 0.5x10⁹/L neutrophils and 20x10⁹/L platelets |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological improvement (HI) (NIH Partial Response)</td>
<td>All of the following: No longer meeting criteria for diagnosis of SAA</td>
<td></td>
</tr>
</tbody>
</table>
| Relapse/progression | Any of the following events after a hematological response (CR or PR): Meeting again the criteria for SAA  
Requirement of transfusion support (if not due to independent medical conditions)  
Decrease in any of the peripheral blood counts as follows:  
Decrease to less than 50% of the medium sustained count during remission if: absolute neutrophils < 1.0 x 10⁹/L, platelets <50 x 10⁹/L; or  
Or in any case if: absolute neutrophils < 0.5 x 10⁹/L, platelets <20 x 10⁹/L  
The peripheral blood count decrease must be:  
not due to any independent concomitant medical condition demonstrated in at least 3 tests over a period of 2 weeks  
not responding to re-introduction of low dose cyclosporin A | |

5. Date best response first observed:

Report the date the best response was first observed. The response date is the date that the sample or image was taken for assessing the response. If the patient is in CR, enter the date CR was achieved or assessed. If the date is unknown, select the Unknown checkbox.
Transfusions since last follow-up

6. RBC

Count and indicate the total number of red blood cells (RBC) units transfused since the last follow-up by ticking an appropriate checkbox:

- < 20 units;
- 20 - 50 units;
- > 50 units.

Select None to mark that there were no RBC transfusions. Answer Unknown if there is no information on RBC transfusions in the patient's medical records.

7. RBC irradiated

Indicate if the RBC were irradiated (answer Yes), not irradiated (answer No) or if it is unknown (answer Unknown).

8. Platelets

Count and indicate the total number of platelets transfused since the last follow-up by ticking an appropriate checkbox:

- < 20 units;
- 20 - 50 units;
- > 50 units.

Select None to mark that there were no platelet transfusions. Answer Unknown if there is no information on platelet transfusions in the patient's medical records.

9. Platelets irradiated

Indicate if platelets were irradiated (answer Yes), not irradiated (answer No) or if it is unknown (answer Unknown).

First relapse after IST

Report the first relapse or progression after the last episode of IST; since multiple IST episodes may be given in an individual patient, relapses after each episode must be reported. If the first relapse/progression was reported at previous follow-up, leave this section without answer and proceed to the last disease status section.
10. First relapse/progression of Aplastic Anaemia (detected by any method):

First relapse means the first relapse that occurs after the first CR or PR has been achieved. If the patient has never had a CR or a PR, the status of the disease cannot be relapse, but it can be progression and thus it is also covered in this section. If a first relapse or progression occurred, select yes. If this did not occur, select no.

10.1. Date of relapse

If the patient had a relapse (not progression) of the primary disease, report the date the relapse was diagnosed.

Disease status at this Follow-Up

11. Disease status at this follow-up:

Select the disease status that reflects the status at the time of this assessment that is being reported. If disease status was not assessed at this follow-up enter Not evaluated.

Complications since last Follow-Up

12. Adverse events/non-infectious complications grade 2-5 observed (based on CTCAE grades):

Check the latest version of Common Terminology Criteria for Adverse Events (CTCAE) available at NCI webpage. Answer Yes if there were any adverse events and non-infectious complications grade 2-5 or mild-very severe observed since the last report. If the adverse event was reported at previous follow up, it is not necessary to report it again.

Answer No if there were no adverse events/non-infectious complications grade 2-5 or mild-very severe observed.

12.1. Observed

If yes was answered to the previous question, indicate per each adverse event/non-infectious complication in the table below if it was observed (answer Yes) or not (answer No). If there was any adverse event/non-infectious complication observed that is not mentioned in the table, check the box Other and specify the event in the text field in English.
12.2. Maximum CTCAE grade

For each adverse event that was observed, select the maximum CTCAE grade that was observed.

12.3. Onset date

For each adverse event that was observed, indicate the onset date of the event.

Secondary malignancies

13. Did a secondary malignancy or autoimmune disorder occur?

Answer No if neither secondary malignancy nor autoimmune disorder has been observed after this IST episode. Answer Yes if secondary malignancy or autoimmune disorder occurred and specify:

13.1. Was this disease an indication for a subsequent HCT/CT/IST?

If the answer is No, complete the respective non-indication diagnosis form.

If the answer is Yes, complete the relevant indication diagnosis form.

Bone marrow investigations

In this section, specify the results of the bone marrow examinations.

14. Bone marrow investigation:

If any bone marrow investigation was performed answer Yes and provide details in subsequent questions of this section. If not, select No and proceed to the next section.

14.1. Date of bone marrow investigation:

Report the date the bone marrow investigation was done.

14.2. Type of bone marrow investigation:

Specify the type of bone marrow investigation performed, whether it was:

- Cytology;
- Histology: or
- Both.
14.3. Type of dysplasia

Indicate per each dysplasia type (Erythroid, Granulocyte and Megakaryocyte dysplasia) if it was detected:

- answer Yes if it was detected at bone marrow investigation; or
- answer No if it was not detected.

If the dysplasia type has not been evaluated, select Not evaluated, and if unknown, answer Unknown.

15. Cellularity in the bone marrow aspirate:

Report the result of the cellularity assessment performed by aspiration test by indicating if the bone marrow was Acellular, Hypocellular, Normocellular, Hypercellular or it had Focal cellularity.

Usually, the examination of the BM aspirate is done by a haematologist. The results can be found in the haematology lab report.

<table>
<thead>
<tr>
<th>Cellularity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acellular</td>
<td>Absence of bone marrow cells (&quot;dry tap&quot;)</td>
</tr>
<tr>
<td>Hypocellular</td>
<td>Bone marrow has fewer cells than normal or expected</td>
</tr>
<tr>
<td>Normocellular</td>
<td>Bone marrow has normal cellularity</td>
</tr>
<tr>
<td>Hypercellular</td>
<td>Bone marrow has more cells than normal or expected</td>
</tr>
<tr>
<td>Focal cellularity</td>
<td>Bone marrow has fewer cells than normal or expected but with the local normal cellularity</td>
</tr>
</tbody>
</table>

Table 2, definitions of bone marrow cellularity

If the cellularity in the bone marrow aspirate was not evaluated, report Not evaluated. Select Unknown in case it is not known if the cellularity was assessed or not.

16. Cellularity in the bone marrow trephine:

Report the result of the cellularity assessment performed by trephine biopsy by indicating if the bone marrow was Acellular, Hypocellular, Normocellular, Hypercellular or it had Focal cellularity (see the table above).

The results of the bone marrow trephine biopsy can be found in the pathology report.

If the cellularity in the bone marrow trephine was not evaluated, report Not evaluated. Select Unknown in case it is not known if the cellularity was assessed or not.
17. Fibrosis on bone marrow biopsy:

Indicate if the bone marrow biopsy revealed any signs of fibrosis. Select No, if the biopsy did not show features of fibrosis. If the biopsy revealed histological features of fibrosis select Mild, Moderate or Severe depending on the fibrosis severity grade.

The results of the bone marrow biopsy can be found in the pathology report.

Check Not evaluable if the sample could not be analysed. If fibrosis was not evaluated, report Not evaluated. Select Unknown in case it is not known if the fibrosis was assessed or not.

18. CD34+ cell count:

Indicate the percentage of CD34+ cells in the bone marrow sample. If the cell count was not assessed, report Not evaluated. Select Unknown in case it is not known if the cell count was measured or not.

19. Blast count:

Indicate the percentage of blast cells in the bone marrow sample. If the cell count was not assessed, report Not evaluated. Select Unknown in case it is not known if the cell count was measured or not.

Chromosome analysis

20. Chromosome analysis done at follow-up (all methods including FISH):

In this section describe the results of the most recent complete chromosome analysis (performed during this follow-up period).

Not done or failed - the chromosome analysis has not been done or failed;

Yes, abnormal results - the chromosome analysis has been performed and at least one of the results has been found to be abnormal. Provide details in subsequent questions of this section.

Yes, normal results - the chromosome analysis has been performed and all the results have been found normal;

Unknown - it is unknown whether the chromosome analysis has been done or not.

If more than one analysis has been done since previous follow up (or since diagnosis for the first annual follow-up), indicate Yes, abnormal results if at least one analysis has been found to be abnormal. In this case, describe the results of the most recent analysis with abnormal results.

21. Date of chromosome analysis (if applicable):

Indicate the date of the chromosome analysis mentioned above.
If the chromosome analysis was not done/failed or it is unknown if it was performed, leave the field blank.

22. **Chromosome analysis details:**

See the cytogenetics form or ask the cytogenetics team and consult your physician.

If chromosome analysis was performed, indicate for each abnormality in the table whether it was **Absent** or **Present**. If a chromosome abnormality was not evaluated, report **Not evaluated**.

If a chromosome abnormality was checked, but not listed as an option in the table, select **Other** and specify the abnormality in the text field, marking whether it was **Absent** or **Present**.

**Molecular marker analysis**

23. **Molecular marker analysis done at follow-up:**

If molecular markers were assessed at this follow-up, select **Yes** and provide details in subsequent questions of this section. If they were not assessed, select **No**. Select **Unknown** if it is unknown whether the analysis of the molecular markers has been done or not.

24. **Date of molecular marker analysis:**

If applicable, report the date of the molecular marker analysis.

25. **Molecular marker analysis details:**

If molecular marker analysis was performed, indicate for each marker in the table whether it was **Absent** or **Present**. If a molecular marker was not evaluated, report **Not evaluated**.

If a molecular marker was evaluated, but not listed as an option in the table, select **Other** and specify the marker, indicating whether it was **Absent** or **Present**.

**PNH Tests at this Follow-Up**

26. **PNH test done:**

Report if PNH test was done in the follow up period or not. If it is not known if the PNH test was performed please select **Unknown**.
26.1. Date of PNH test:

If the answer to the previous question is **Yes**, indicate the date of the PNH test. In case the date is not known, report **Unknown**.

26.2. PNH diagnostics by flow cytometry:

Indicate if clone was absent or present by selecting the respective check box, or mark it as **Not evaluated** if applicable.

If the **Clone present** option is selected, specify also the **Size of the clone** in % (PNH clone size refers to the proportion of PNH-affected cells versus normal cells within the total cell population). This information can be found in the haematology report.

26.3. Flow cytometry assessment done on:

Check the corresponding check box to indicate if **Granulocytes**, red blood cells (**RBC**) or **Both** were analysed by flow cytometry. If flow cytometry was done on other cells, select **Other** and specify the cell type in English.

26.4. Clinical manifestation of PNH:

If there are any clinical manifestations of PNH, select **Yes**, if not, select **No**.

You can find more details on PNH manifestation in the bone marrow failures completion guidelines.

26.5. Date of clinical manifestation of PNH

If the answer to the previous question is **Yes**, report the date when the clinical manifestation was first reported. In case the date is not known, report **Unknown**.

26.6. Anti-complement treatment given?

Indicate if any anti-complement treatment was given to the patient by selecting either **No** or **Yes**. Including compounds that inhibit the complement system, for example: C-5 inhibitors (Eculizumab & Ravulizumab) and C-3 inhibitors (Pegcetacoplan). If the anti-complement treatment that has been given is not listed please select: **Other; specify**.

If anti-complement treatment was given, provide details.

26.6.1. **Drug:**

Select the drug name from the list of options or use **Other** field and report the generic drug/agent name(s) in the textbox in English.

Please consult the List of Chemotherapy Drugs, Agents and Regimens on the EBMT website for drug/agent names. This document provides alternative names for many of the drugs/agents.

Once you have found the drug/agent of interest on the list, add its database name to the table.
26.6.2. **Start date:**

Indicate the date when the treatment was started. In case the date is not known, report **Unknown**.

26.6.3. **Stop date:**

Indicate the date when the treatment was stopped. If the treatment is still in progress, select **Ongoing**. In case the date is not known, report **Unknown**.

If there were more drugs given during one line of treatment use copies of the page for the paper form. It is also possible to add additional fields in the online EBMT Registry application to report multiple drugs here.

## Cause of Death (if patient died)

27. **Main cause of death:**

Check only one main cause that applies. In case of doubt, consult a physician. If none of the answers in the table match, tick the box **Other** and specify it. If the cause of death is not known, select **Unknown**.

The following main causes of death can be reported (check only one):

- **Relapse or progression/persistent disease**;
- **Secondary malignancy**;
- **Cellular therapy-related** - death caused by complications or infections after cellular therapy (also indicate the treatment related cause);
- **HCT-related** - death caused by complications or infections after transplant (also indicate the treatment related cause);
- **IST-related** – death caused by complications or infections after an immunosuppressive episode (also indicate the treatment related cause).

27.1. **Select treatment related cause:**

In case of Cellular therapy- or HCT-related cause of death, specify if the cause of death was related to:

- **Graft versus host disease (GvHD)**;
- **Non-infectious complication**;
- **Infectious complication**.

27.1.1. **Infectious complication:**

If the cause of death was related to an infectious complication, select the type(s) of infections that apply:

- **Bacterial infection**;
- **Viral infection**;
- **Fungal infection**;
- Parasitic infection;
- Infection with unknown pathogen.