

Recommendations for the management of patients with AML during the COVID19 outbreak:
a statement from the NCRI AML Working Party

The COVID 19 outbreak will cause major capacity pressures within the NHS. In light of the multiple emerging pressures within the NHS the NCRI AML working group has consulted widely in order to identify treatment strategies in adults with newly diagnosed AML which reduce NHS pressure whilst preserving patient outcomes. Mindful of the pace of change these recommendations will undergo regular review and should be considered valid until 5th April 2020. The aim of these guidelines is to suggest practical ways to protect patients with AML and reduce impact on bed and intensive care capacity by reducing treatment intensity or length where it is reasonably safe to do so. These recommendations should be interpreted in the context of local Trust specific guidance and take into account guidance already issued by NICE, NHS England and other relevant organisations. They are only valid in the setting of the current COVID pandemic. Separate guidelines for stem cell transplantation are available at bsbmtct.org.

1. General points

- All patients receiving intensive therapy should, where possible, be barrier nursed in a single room.
- All patients should be screened for COVID-19 before initiation of induction or consolidation chemotherapy.
- Please notify us if you have a patient with AML who is diagnosed with COVID19 so we can start to collect outcome data for these patients (email richarddillon@nhs.net).
- We recommend waiting for cytogenetics and *NPM1/FLT3* status before treatment where possible.
- MRD monitoring may be particularly helpful during this outbreak. Flow MRD monitoring may be performed without a baseline sample, however this is needed for molecular MRD. To allow quick turnaround of molecular MRD status please ensure a baseline cDNA sample is sent from the local diagnostic lab to Guy's as soon as a molecular marker is identified (any fusion gene or *NPM1* mutation).

2. Intensive treatment for adults aged <60y

Patients with favourable (i.e. t(8;21) and inv(16) – CBF AML) and intermediate risk cytogenetics:

- These patients should receive DA with a single dose of Mylotarg with their first course of induction chemotherapy. The exception to this is patients with a *FLT3* mutation receiving midostaurin during induction who should not receive Mylotarg at all.
- Mylotarg should be given to all CBF-AML patients. They should not receive midostaurin with induction even if *FLT3* mutated. If Mylotarg supplies run low it may be necessary to restrict Mylotarg to CBF-AML patients.
- Mylotarg is not recommended in cycle 2 or subsequent cycles of chemotherapy since it can delay count recovery and is of uncertain benefit.
- In patients who are MRD negative in the bone marrow after the second cycle of treatment (by flow or molecular methods), consideration should be given to omitting the 4th cycle of chemotherapy. In this case post course 3 samples for MRD evaluation are mandatory and, for patients with a molecular marker, sequential monitoring is recommended.
- The dose of cytarabine in consolidation chemotherapy should be reduced to 1.5g/m² for all patients. This is associated with faster count recovery than the standard dose with no effect on overall survival.
- These measures, which reduce exposure to cytarabine during consolidation, may modestly reduce relapse free survival but are not predicted to decrease overall survival if effective salvage strategies are deployed. Therefore, careful molecular monitoring should be adopted in all eligible patients with an informative marker, with pre-emptive intervention in patients with molecular relapse.

Patients with a NPM1^{mut}/FLT3 ITD^{neg} genotype:

- This population of patients achieve a high rate of durable CR if treated with venetoclax (VEN) based non-intensive regimens (see page 3). VEN based regimens should therefore be considered as an alternative to induction chemotherapy for these patients, particularly those aged >50 with comorbidities. Stringent molecular monitoring for *NPM1* transcripts is mandatory if such a strategy is adopted. This approach is also recommended for patients with this genotype with molecular or haematological relapse.

Patients with adverse risk cytogenetics:

- These patients should not receive Mylotarg.
- Many such patients may be eligible for treatment with CPX351.

3. Intensive treatment for adults aged >60y

Patients with favourable risk cytogenetics (i.e. t(8;21) and inv(16) – CBF AML):

- These patients should receive intensive therapy with a single dose of Mylotarg in induction.
- They should not receive midostaurin even if *FLT3* mutated.

- They should receive 1.5g/m² cytarabine in consolidation and could omit the fourth cycle of consolidation if MRD negative by RT-qPCR in a sample affording adequate sensitivity after cycle 2 as described above, they should receive careful sequential molecular MRD monitoring after completion of treatment.

Patients with intermediate risk cytogenetics

- These patients may still enter AML18 if your hospital allows this. AML18 allows access to CPX351 for 66% of patients. Of note trial capacity across the NHS has been significantly reduced at the present time.
- Although standard of care would be DA+GO, consider omitting Mylotarg altogether for these patients currently. If patients are later found to have favourable risk cytogenetics then a single dose can be given with cycle 2.
- Treatment with a VEN based regimen should be considered for these patients as an alternative to induction chemotherapy, particularly if they have *NPM1* or *IDH2* mutations which are associated with a very high complete response rate. Discussions are ongoing with Abbvie and NHS England to explore the possibility of obtaining commissioning approval for this therapeutic option as an emergency measure (see page 3). Stringent molecular monitoring is mandatory for *NPM1*^{mut} (relevance of monitoring *IDH2* mutations remains uncertain). Intensification with chemotherapy and or transplant may be required later on during the treatment pathway however it is hoped that this could be deferred until the epidemic has passed.

Patients with adverse risk cytogenetics

- These patients should not receive Mylotarg.
- Many such patients may be eligible for treatment with CPX351.
- There may be a case for considering a VEN based regimen in these patients. The data are sparse and the follow up is short but the CR rates may be comparable and this may allow patients to receive out-patient therapy. It is unclear if either VEN-AZA or VEN-LDAC is the superior combination for this patient group.

4. Patients with APL

- **Patients with non-high-risk APL** (presenting white blood cell count <10x10⁹/L) should continue to receive ATO+ATRA as frontline therapy. We recommend the AML17 schedule which requires fewer hospital visits.
- If these patients are MRD negative after the second cycle, consideration should be given to omission of the final (5th) cycle of treatment. These patients would need to have ongoing MRD monitoring.
- **Patients with high-risk APL** should continue to receive AIDA as induction, but could switch to ATO+ATRA for consolidation and should receive all four consolidation cycles with ongoing MRD monitoring.

5. Possible future changes

The situation will be kept under close review and the guidance provided here will be updated regularly. In light of the possibility that acute capacity constraints may severely limit the future ability of intensive chemotherapy contact has been made with NHS England and the relevant pharmaceutical companies to explore the possibility of more widespread adoption of VEN based regimens as an up-front treatment strategy in newly diagnosed AML as well as utilising Gilteritinib, Ivosidenib and Enasidenib as salvage strategies in relapsed AML with targetable mutations. These agents are currently not routinely commissioned but if supplies can be secured advice on their deployment will be included in future versions of this document.

6. Writing group membership and contacts for clinical and MRD advice

These recommendations represent the opinions of a subgroup of the NCRI AML Working Party (Chair Charles Craddock) and have been coordinated by Richard Dillon working with Paul Cahalin, Jamie Cavenagh, Charles Craddock, Mike Dennis, Sylvie Freeman, Asim Khwaja, Steven Knapper, Tony Pagliuca, Nigel Russell, David Taussig and Paresh Vyas.

Clinical questions regarding all aspects of the AML 18 and 19 trials should be referred, as is normal practice, to the current AML 18 and 19 trial leadership team as outlined in the respective protocols.

For additional questions concerning non-trial management issues the following members of the AML Working Party are happy to be contacted for advice:

Richard Dillon (richarddillon@nhs.net), Charles Craddock (Charles.Craddock@uhb.nhs.uk), Mike Dennis (Mike.Dennis@christie.nhs.uk), Sylvie Freeman (s.freeman@bham.ac.uk), Steven Knapper (knappers@cardiff.ac.uk) Nigel Russell (Nigel.Russell@nottingham.ac.uk), and Paresh Vyas (paresh.vyas@imm.ox.ac.uk)

Use of Venetoclax based regimens in place of intensive therapy during the COVID19 outbreak

Venetoclax (VEN) based treatment protocols produce significantly lower toxicity compared to intensive therapy. Treatment is largely delivered as an outpatient. Remission rates are close to those achieved with intensive therapy. The use of VEN based regimens is therefore attractive both to reduce pressure on the NHS and protect patients at especially high risk during the COVID19 outbreak.

Long-term follow up data are immature and in general the approach we recommend is to use VEN to bridge patients through the COVID19 epidemic with a view to delivering definitive therapy possibly including transplant later on. Decisions regarding subsequent treatment should be made on a case by case basis and MRD status will be particularly informative in this regard.

At the time of writing (23rd March 2020) universal free drug supply through NHS England has not been agreed. However, this remains under discussion and further guidance will be issued if this changes. Some centres have taken a local decision to use VEN on an emergency basis during the COVID19 epidemic. The cost of delivering the below schedule is around £850 per month, this is significantly below the cost of delivering a cycle of intensive therapy and importantly also significantly reduces the pressure on in-patient and ITU beds. However, VEN is not currently reimbursed.

If VEN can be accessed through local or NHSE approval this should be considered for the following patients:

- Any non-CBF patient aged >60y or with significant comorbidities
- Patients with an *NPM1* or *IDH2* mutation aged >50y or with comorbidities
- Patients with the *NPM1*^{mut} *FLT3* ITD^{neg} genotype of any age (but particularly those aged >50y or with comorbidity)

The following treatment schedule is recommended:

- Admit to hospital for at least 5 days during the first cycle (subsequent cycles given as outpatient)
- Cytarabine 20mg/m² once a day on D1 to 10 or Azacitidine 75mg/ m². once a day D1-7 (or D1-5 and D8-9)
- Venetoclax 10mg D1, 20mg D2, 50mg D3, 100mg D4-D28 orally, once daily (cycle 1)
- 100mg D1-D28* orally, once daily (cycle 2 onwards) (*if responding may reduce to 21 or 14 days)
- Aciclovir 400mg twice a day D1-28 (**mandatory**)
- Either posaconazole 300mg twice a day on D1 and once a day on D2-28 or voriconazole 400mg twice a day on D1 and 200mg twice a day on D2-28 (**mandatory**)

Dose adjustments for haematological toxicity:

- VEN based regimes are associated with significant haematological toxicity
- VEN should not be interrupted *during* a treatment cycle for haematological toxicity
- Commence next cycle when neutrophil count > 1x10⁹/L and platelet count >75 x10⁹/L
- If counts have not recovered above these levels by D42 please do a bone marrow aspirate
- For patients in complete remission, if grade 4 haematological toxicity persisted beyond day 42 of the previous cycle, the duration of VEN may be reduced from 28 days to 21 days. Further recommendations about VEN dosing will be issued in subsequent guidelines.
- If grade 4 haematological toxicity still persists beyond day 42 of subsequent cycles, the duration of VEN can be reduced further to 14 days. If using azacitidine the length of treatment could also be reduced to 5 days.
- In patients who have not yet been confirmed to be in complete remission the length of subsequent treatment cycles should not be altered.
- Patients who do not achieve CR after cycle 2 should be discussed at an MDT.

Dose adjustments for non-haematological toxicity:

- In patients with grade 3-4 abnormal liver function tests (i.e. alanine aminotransferase [ALT] aspartate aminotransferase [AST] and bilirubin), VEN and any potentially hepatotoxic drugs (including azole antifungals) should be withheld until these have resolved to grade 2 or below and then VEN (and the azole antifungal if applicable) should be restarted at the original dose.
- VEN should not be interrupted for any other non-haematological toxicity for patients who are not in complete remission.
- In patients in complete remission with grade 3 or 4 non-haematological toxicity thought to be related to VEN, this should be withheld until the toxicity has resolved to grade 2 or below and then restarted at the original dose.