ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CENTRAL PROTOCOL OPERATIONS PROGRAM

MEMORANDUM

To: Principal Investigators, Responsible Investigators, and Alliance Statistics and Data Management Center

From: **Heidi D. Finnes, PharmD, BCOP, FHOPA, Alliance Pharmacy Committee Chair**

Subject: Nationwide Intravenous Leucovorin Shortage affecting A021502, A021703, A021806, and A041501

Date: 15 December 2021

There currently is a nationwide shortage of intravenous (IV) leucovorin. Your institution may or may not be able to obtain sufficient leucovorin for patients enrolled on Alliance trials. The Alliance is issuing the following study-specific plans for the protocols listed below within each committee in the event that individual institutions are not able to obtain IV leucovorin. If a decision is made to use an alternative formulation of leucovorin or to omit one or more leucovorin dose(s), your IRB of record should be notified.

Please visit the following website(s) for updates on leucovorin supply:

- https://www.ashp.org/drug-shortages/current-shortages/drug-shortages-list?page=CurrentShortages
- http://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Leucovorin%20Calcium%20Lyophilized%20Powder%20for%20Injection&st=c&tab=tabs-1

NOTE: Dose modifications of leucovorin up to and including omission of leucovorin or its analogues imposed by drug shortages will not constitute protocol violations. The reason/rationale for modification should be clearly documented in the patient's research chart.

Gastrointestinal Committee:

- **A021502:**
  For practices experiencing shortage of IV racemic leucovorin who wish to enroll new patients to A021502, we recommend (in order of preference):
  - (1) Substitute IV levoleucovorin (at a dose of 200 mg/m^2 or 50% of the protocol-specified dose IV racemic leucovorin) for IV racemic leucovorin. Change to protocol-specified racemic leucovorin when supplies become available.
    OR
  - (2) Substitute a lower dose of IV racemic leucovorin (20 mg/m^2) for the standard dose of 400 mg/m^2. Change to the protocol-specified dose when supplies become available.
    OR
  - (3) If neither racemic leucovorin nor levoleucovorin are available at any dosage, treatment without leucovorin would be acceptable, but this should be re-addressed with each treatment.

  Consideration of these alternatives to standard leucovorin treatment should also be given for patients already receiving treatment.

  In all cases (new or existing patients), the decision to employ an alternative to protocol-specified leucovorin should be made on a dose-by-dose basis.

  If you have any questions or concerns, please contact the Alliance Protocol Coordinator and the respective Study Chair.

- **A021703:**
  For practices experiencing shortage of IV racemic leucovorin who wish to enroll new patients to A021703, we recommend (in order of preference):
    - (1) Substitute IV levoleucovorin (at a dose of 200 mg/m^2 or 50% of the protocol-specified dose IV racemic leucovorin) for IV racemic leucovorin. Change to protocol-specified racemic leucovorin when supplies become available.
      OR
    - (2) Substitute a lower dose of IV racemic leucovorin (20 mg/m^2) for the standard dose of 400 mg/m^2. Change to the protocol-specified dose when supplies become available.
      OR
    - (3) If neither racemic leucovorin nor levoleucovorin are available at any dosage, treatment without leucovorin would be acceptable, but this should be re-addressed with each treatment.

  Consideration of these alternatives to standard leucovorin treatment should also be given for patients already receiving treatment.

  In all cases (new or existing patients), the decision to employ an alternative to protocol-specified leucovorin should be made on a dose-by-dose basis.

  If you have any questions or concerns, please contact the Alliance Protocol Coordinator and the respective Study Chair.

- **A021806:**
  For practices experiencing shortage of IV racemic leucovorin who wish to enroll new patients to A021806, we recommend (in order of preference):
    - (1) Substitute IV levoleucovorin (at a dose of 200 mg/m^2 or 50% of the protocol-specified dose IV racemic leucovorin) for IV racemic leucovorin. Change to protocol-specified racemic leucovorin when supplies become available.
      OR
    - (2) Substitute a lower dose of IV racemic leucovorin (20 mg/m^2) for the standard dose of 400 mg/m^2. Change to the protocol-specified dose when supplies become available.
      OR
    - (3) If neither racemic leucovorin nor levoleucovorin are available at any dosage, treatment without leucovorin would be acceptable, but this should be re-addressed with each treatment.

  Consideration of these alternatives to standard leucovorin treatment should also be given for patients already receiving treatment.

  In all cases (new or existing patients), the decision to employ an alternative to protocol-specified leucovorin should be made on a dose-by-dose basis.

  If you have any questions or concerns, please contact the Alliance Protocol Coordinator and the respective Study Chair.

Leukemia Committee:

- **A041501 (when leucovorin is required after high-dose methotrexate therapy):** For patients who develop methotrexate toxicity with prolonged evaluations of plasma methotrexate levels, alternative forms of leucovorin including levoleucovorin or oral leucovorin may be substituted for racemic leucovorin in addition to standard supportive care measures until MTX level is <0.1 umol/L.