



ADVANCED MEDICAL STRATEGIES
PHYSICIANS. TAKING CARE OF BUSINESS.

February 11, 2015

Upon request of ABC a medical opinion regarding the treatment provided was conducted on the above patient. Our findings are documented below:

Clinical Summary:

The patient is a 33-year-old male with T-cell lymphoblastic leukemia/lymphoma who underwent induction therapy per CALGB 10403 protocol. The patient was diagnosed 5/20/13 after developing back pain and weakness of the left leg. He was found to have an epidural mass from T4 to T8 (thoracic) and underwent surgical decompression. The pathology revealed the diagnosis and he was initiated on steroids with staging studies revealing mediastinal adenopathy without bone marrow involvement. He has received intrathecal therapy and subsequently was started on systemic therapy per CALGB 10403 (off study). Treatment is under review.

Questions:

- 1. Please briefly describe the CALGB 10403 protocol.**
- 2. Based upon your experience, your review of the medical records, and your knowledge of the diagnosis and patient condition, is the CALGB 10403 protocol treatment (or modified version) which this claimant received considered to be Experimental/Investigational? Please explain your answer.**
- 3. Based upon your review of the wording in the Summary Plan Description, is the CALGB 10403 protocol treatment (or modified version) which this claimant received considered to be Experimental/Investigational? Please explain your answer.**
- 4. Based upon your review of the wording in the Stop Loss Policy, is the CALGB 10403 protocol treatment (or modified version) which this claimant received considered Experimental/Investigational?**

Conclusions*:

- 1. Please briefly describe the CALGB 10403 protocol.**

This study uses multi agent chemotherapy and radiotherapy in the treatment of ALL (acute lymphoblastic leukemia). The agents utilized are cyclophosphamide (CTX), cytarabine (ARA-C), daunorubicin (DRC), dexamethasone (DEX), doxorubicin (ADRIA), mercaptopurine (6-MP),

methotrexate, (MTX) peg-asparaginase (PEG-ASNASE), thioguanine (6-T6), and vincristine (VCR).

The following is the schedule: (D = Day)

Remission induction (extended remission induction also given to some patients, depending on D29 BMBx [bone marrow biopsy]) – four wk (week) Intrathecal Ara-C (D1)

Intrathecal MTX (D8, 29)

Prednisone (D1-28)

Vincristine (D1, 8, 15, 22)

Daunorubicin (D1, 8, 15, 22)

Peg-asparaginase (D4)

Remission consolidation eight wk Intrathecal MTX (D1, 8, 15, 22)

Cyclophosphamide (D1, 29)

Ara-C (D1-4, 8-11, 29-32, 36-39)

6-MP (D1-14, 29-42)

Vincristine (D15, 22, 43, 50)

Peg-asparaginase (D15, 43)

Interim maintenance eight wk Intrathecal MTX (D1, 31)

Vincristine (D1, 11, 21, 31, 41)

Methotrexate (D1, 11, 21, 31, 41)

PEG-asparaginase (D2, 22)

Delayed intensification eight wk Intrathecal MTX (D1, 29, 36)

Dexamethasone (D1-7, 15-21)

Doxorubicin (D1, 8, 15)

Peg-asparaginase (D4, 43)

Cyclophosphamide (D29)

Ara-C (D29-32, 36-39)

6-TG (D29-42)

Maintenance Repeated 12-wk courses

Intrathecal MTX (D15, and D29 of first four courses of maintenance)

Total duration of maintenance: Three years from IM (induction maintenance) for males

Vincristine (D1, 29, 57)

6-MP (D1-84)

Methotrexate (D8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78; held on D29 of first 4 courses of maintenance when IT is given)

2. Based upon your experience, your review of the medical records, and your knowledge of the diagnosis and patient condition, is the CALGB 10403 protocol treatment (or modified version) which this claimant received considered to be Experimental/Investigational? Please explain your answer.

Yes. All of the agents in this regimen are recommend by the NCCN (National Comprehensive Cancer Network) and are included in the ALL Guidelines, however the schedule is not the same as standard adult induction regimens. The purpose of CALGB 10403 is to evaluate whether adolescents and young adults (AYAs) benefit from a pediatric approach to the disease as opposed to the standard approach. Wood, et al. state "...There are no prospective studies that demonstrate that an adult-like or pediatric-like therapeutic approach is superior for AYAs with

Philadelphia chromosome–negative ALL. However, multiple retrospective studies suggest that a pediatric-like approach may be superior in this patient population, and several cohort studies are beginning to demonstrate the feasibility of this approach..." This CALGB trial included patients from age 16 to 39. The authors of Up-To-Date state "... Several retrospective comparative analyses have reported that young adults/adolescents with ALL treated on pediatric protocols demonstrate superior event-free and overall survival rates when compared with similar patients enrolled on adult ALL protocols.." As this approach, while promising, remains the subject of ongoing investigation and is not formally recommended in the peer-reviewed literature, by the authors of Up-To-Date, nor by the NCCN guideline, it would meet plan criteria for experimental therapy.

- 3. Based upon your review of the wording in the Summary Plan Description, is the CALGB 10403 protocol treatment (or modified version) which this claimant received considered to be Experimental/Investigational? Please explain your answer.**

As this approach remains the subject of ongoing investigation for efficacy (NCT00558519), it is considered experimental based on the SPD (summary plan description).

- 4. Based upon your review of the wording in the Stop Loss Policy, is the CALGB 10403 protocol treatment (or modified version) which this claimant received considered Experimental/Investigational?**

As this approach remains the subject of ongoing investigation for efficacy (NCT00558519), it is considered experimental based on the SLP (stop loss policy).

Reference(s):

1. Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia. ClinicalTrials.gov. Service of U.S. National Institutes of Health. <http://clinicaltrials.gov/ct2/show/NCT00558519?term=CALGB+10403&rank=1>
2. Acute Lymphoblastic Leukemia. Version 3.2013. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/all.pdf
3. Wood WA, et al. Malignant hematologic diseases in adolescents and young adults. Blood. June 2, 2011 vol. 117 no. 22 5803-5815. <http://bloodjournal.hematologylibrary.org/content/117/22/5803/T3.expansion.html>
4. Larson RA, Induction therapy for Philadelphia chromosome negative acute lymphoblastic leukemia in adults. Up-To-Date. Literature review current through Apr 2014. Topic last updated Apr 29 2014.

Reviewer's Credentials

Is board certified in medical oncology and hematology with an active practice at regional medical centers. Published in peer reviewed literature and books. Is active in the field of research and professional societies. Lectures by invitation.

**The conclusions in this report may be modified or updated if additional historical or analytical data becomes available. The recommendations noted are made to a reasonable degree of medical certainty. These opinions are based on the medical records and information submitted to AMS for review, Physician/clinician contractors also consider published scientific medical evidence and other relevant information such as that available through federal government agencies, institutes, and professional associations. Advanced Medical Strategies, LLC. assumes no liability for the opinions. The client authorizing this case review agrees to hold AMS harmless for any and all claims which may arise as a result of this case review. This opinion is not intended to be final interpretation of plan/policy language or determination of benefits or exclusions. Adjudication of the claim remains solely the client's responsibility.*

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