Prognostication

Question 1

A 66-year-old woman is evaluated for progressive fatigue and bilateral painful swelling in her axillae. Her medical history includes hypertension, depression, and rheumatoid arthritis. Physical examination shows axillary lymphadenopathy and splenomegaly. The patient is ambulatory but is limited in strenuous activity.

Laboratory evaluation shows:

Hemoglobin	9.0 g/dL
Leukocyte count and differential	32,000/µL with 90% lymphocytes
Platelet count	95,000/µL
Serum creatinine	0.9 mg/dL

Molecular cytogenetic analysis shows del(17p); *TP53* wild type, and *IGHV* mutated.

The patient is diagnosed with chronic lymphocytic leukemia Rai stage IV and Binet stage C.

Which one of the following statements about this patient's risk status is true?

A. The patient has high-risk disease because of the *IGHV* mutation
B. The patient has high-risk disease because of the presence of del(17p)
C. The patient has intermediate-risk disease because of the presence of *TP53* wild type
D. The patient has intermediate-risk disease because of Rai/Binet staging

The correct answer is: B (The patient has high-risk disease because of the presence of del(17p))

Answer rationale:

- Patient has high-risk CLL. High risk cytogenetics for CLL include del(17p), *TP53* mutation, and *IGHV* unmutated
- Del(17p) presence has a significant impact on progression-free survival resulting in a poor prognosis for patients with CLL with del(17p), especially with historical chemoimmunotherapy treatment options.
- BTK inhibitors have shown improved outcomes in patients with del(17p) CLL.
- It is important to evaluate prognostic factors, including cytogenetics, in patients with CLL and communicate the prognostic values and implications as they relate to patient outcomes and treatment considerations.
- Patients with del(17p) and *TP53* mutations exhibited shorter PFS rates on frontline BCL-2 based therapy with venetoclax plus obinutuzumab than data reported with frontline continuous BTK inhibitor-based treatments (cross trial nonrandomized comparisons). Therefore, continuous therapy with BTK inhibitors should be considered in frontline CLL in the presence of *TP53* disruption (either del(17p) by FISH or *TP53* mutation), in the absence of any major contraindications to BTKi therapy.

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Question 2

Which one of the following statements about *TP53* mutations in patients with CLL is true?

A. *TP53* mutations can occur in the absence of del(17p)
B. *TP53* mutations correlate with improved median survival and increased response to treatment
C. *TP53* mutations with mutated *IGHV* genes are associated with worse progression-free survival and overall survival than *TP53* mutations with unmutated *IGHV* genes
D. *TP53* mutation status does not change over the course of disease

The correct answer is: A (*TP53* mutations can occur in the absence of del(17p))

Answer rationale:

- *TP53* gene abnormalities can occur in the absence of del(17p) and *TP53* mutations have been identified as predictors of resistance to chemoimmunotherapy based regimens leading to poor survival and outcomes (independent of 17p chromosome status). Approximately 5%-8% patients with CLL have a TP53 mutation (identified only on Sanger sequencing or next generation sequencing) in the absence of del(17p) by FISH.
- *TP53* mutations are a strong prognostic indicator of high-risk features in CLL. *TP53* wild-type status for a patient would correlate to favorable risk profile and likely improved outcomes.
- *IGHV* mutation status does not change over time and analysis does not need to be repeated if previously done prior to initiation of treatment. Del(17p) and *TP53* abnormalities can change over the course of the disease and so reassessment prior to each treatment course is required.
- While historical chemoimmunotherapy regimens (BR, FCR, chlorambucil ± obinutuzumab) have fared poorly in patients with high-risk features such as *TP53* mutations and del(17p); BTK inhibitors and BCL-2 inhibitors result in better outcomes even in patients with high-risk features with consistent PFS benefit seen in patients with or without these high-risk features.

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MRD – Sensitivity and interpreting MRD status

Question 3

Which one of the following statements about testing for minimal residual disease (MRD) in chronic lymphocytic leukemia (CLL) is true?

A. Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) cannot detect MRD in CLL
B. Flow cytometry–based MRD testing for CLL is more expensive and labor-intensive resulting in less utilization
C. MRD testing is not an appropriate tool for CLL response assessment because of lack of validation
D. Next-generation sequencing (NGS)-based assays are more sensitive than PCR and flow cytometry for detecting MRD in CLL

The correct answer is: D (Next-generation sequencing (NGS)-based assays are more sensitive than PCR and flow cytometry for detecting MRD in CLL)

Answer rationale:

- Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and flow cytometry (MRD flow) are the 2 validated methods used for the detection of MRD at the level of 10^{-4} to 10^{-5}.
- Next-generation sequencing (NGS)-based assays, such as ClonoSEQ®, have been shown to be more sensitive, thus allowing for the detection of MRD at the level of 10^{-6}.
- MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method; and as per the 2018 iwCLL guidelines.
- ASO-PCR detects MRD (at the level of $<10^{-5}$); however; it is less widely used since it is expensive and more labor intensive.
- Although more sensitive techniques to detect MRD are available, current data support the continued use of 1 $x10^{-4}$ as the threshold for MRD, in line with the 2018 iwCLL guidelines.

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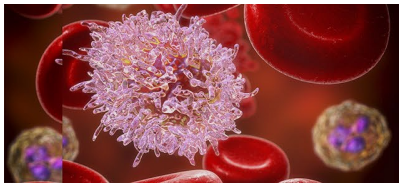

MUTATIONS, SEQUENCING, RESISTANCE: ADVANCES AND UPDATES IN CHRONIC LYMPHOCYTIC LEUKEMIA

Interpreting MRD status

Question 4

A 59-year-old woman with a history of relapsed/refractory chronic lymphocytic leukemia is evaluated for response to recently completed 2 years of therapy with venetoclax plus rituximab. She had initially received fludarabine, cyclophosphamide, and rituximab (FCR) 6 years ago and achieved a complete response before relapse occurred and venetoclax-based therapy was begun. The patient's medical history includes osteoarthritis and well-controlled hypertension. CLL cytogenetics obtained on initial diagnosis revealed no del(17p) present, *TP53* wild type, & *IGHV* mutated.

On physical examination, the patient feels well with good energy level. Laboratory evaluation shows:

Hgb	13 g/dL
Leukocyte count and differential	8,000/µL with 40% lymphocytes
Platelet count	125,000/µL
Serum creatinine	1.0 mg/dL

At follow-up visit, minimal residual disease (MRD) results by next generation sequencing show low MRD positivity ($\geq 10^{-4}$ to 10^{-2}).

Which one of the following is the most appropriate management for this patient at this time?

A. Start triplet therapy with venetoclax, obinutuzumab, and ibrutinib
B. Monitor for disease progression, without further treatment
C. Reinitiate venetoclax maintenance therapy
D. Start third-line pirtobrutinib therapy

The correct answer is: B (Monitor for disease progression, without further treatment)

Answer rationale:

- Patient appears to have achieved a good response to second-line therapy with venetoclax based on hematologic response. However, MRD results show patient did not achieve MRD negativity but instead has low MRD positivity (≥10-4 to 10-2).
- Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of fixed duration treatment is an important predictor of efficacy.
- MRD is a highly sensitive indicator of disease burden in patients with CLL.
- Patients with undetectable MRD status after completion of fixed duration venetoclax-based combination regimens is a predictive marker for PFS. MRD assessment is a useful tool in clinical practice to provide insight into anticipated PFS duration following fixed duration treatments.
- Based on the MURANO trial, patients with relapsed/refractory CLL who achieve undetectable MRD levels (<10-4), PFS was significantly higher at 24 months (85.4%) and 36 months (61.3%) than those who had low (52.2% at 24 months and 40.7% at 36 months) or high (8.3% at 24 months) MRD positivity.
- However, MRD status is not an appropriate marker to utilize for treatment duration or treatment decisions and additional treatment interventions should not be made based on MRD results at this time. Therefore, observation without any further treatment is the appropriate choice at this time.
- In select patients with persistent MRD after 2 years of venetoclax based treatment who have del17p or TP53 mutation, single agent venetoclax may be continued (note venetoclax is approved by the FDA as continuous therapy for relapsed/refractory del(17p) CLL).

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BTK frontline with high-risk features

Question 5

A 60-year-old man is evaluated for progressive fatigue, dizziness, and swelling of the axillary lymph nodes. His medical history includes hypertension, depression, anxiety, and dyslipidemia. Current list of medications includes lisinopril, hydrochlorothiazide, rosuvastatin, duloxetine, and alprazolam.

On physical examination, he has axillary lymphadenopathy.

Laboratory evaluation shows:

Hemoglobin	9.5 g/dL
Leukocyte count and differential	80,000/µL with 72% lymphocytes
Platelet count	98,000/µL
Serum creatinine	0.8 mg/dL

Cytogenetic analysis shows CD5+, CD20dim, CD23+, CD19+ by flow cytometry; del(17p) and TP53 detected.

Chronic lymphocytic leukemia is diagnosed.

Which one of the following is the most appropriate first-line therapy for this patient?

A. Acalabrutinib
B. Bendamustine plus rituximab
C. Obinutuzumab plus chlorambucil
D. Venetoclax plus ibrutinib

The correct answer is: A (Acalabrutinib)

Answer rationale:

- The patient has high-risk CLL based on cytogenetics, including del(17p) and *TP53* mutation. Standard preferred first-line therapy for high-risk CLL disease with del(17p) and/or *TP53* mutation is a second-generation covalent BTK inhibitor (acalabrutinib or zanubrutinib) per NCCN guidelines given in continuous fashion due to the aggressiveness of disease.
- Ibrutinib may be considered as well as a single agent but most patients will benefit from a second-generation BTK inhibitor (such as zanubrutinib or acalabrutinib) and tolerate it better.
- Venetoclax plus ibrutinib is an emerging combination therapy, but currently only has a category 2B recommendation per NCCN and would not be the most appropriate regimen based on the long-term data currently favoring single agent BTK inhibitor or adding obinutuzumab to acalabrutinib if clinically appropriate. Venetoclax plus obinutuzumab is also a preferred regimen. However, due to the high-risk nature of disease and clinical trial data supporting continuous BTK treatment with potential for improved outcomes compared to fixed duration venetoclax-based regimens in patients with del(17p), a BTK inhibitor will likely be the most appropriate treatment in this setting.
- Chlorambucil and chemoimmunotherapy regimens, such as bendamustine plus rituximab, have fallen out of favor in CLL due to the practice changing outcomes of the BTK inhibitor class.
- Long-term positive data over 10 years with Ibrutinib (ASH 2023 Itsara) in general and in high-risk disease (del(17p) and TP53 mutation)
- Long-term positive data also available with newer generation BTK inhibitors (acalabrutinib and zanubrutinib) and efficacy in high-risk disease

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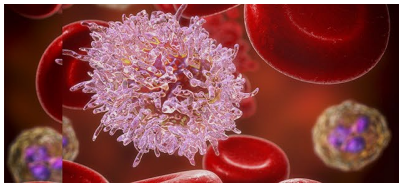

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BTK toxicity

Question 6

A 54-year-old woman is evaluated by her primary care physician for routine annual follow-up. She is noted to have an irregular heart rhythm. She is completely asymptomatic. Electrocardiography confirms atrial fibrillation. The patient is evaluated by cardiology; and given the low risk of stroke, anticoagulation is not indicated; and rate control strategy alone with metoprolol is started.

The patient's medical history includes hypothyroidism and controlled hypertension. Six months prior, she was diagnosed with *TP53*-mutated and *IGHV*-mutated chronic lymphocytic leukemia. Therapy with ibrutinib, 420 mg/day, was started and the patient achieved a partial response; and is otherwise tolerating the treatment well.

Which one of the following is the most appropriate therapy for this patient with CLL leukemia at this time?

A. Switch to acalabrutinib plus obinutuzumab
B. Switch to pirtobrutinib
C. Switch to venetoclax plus rituximab
D. Reduce dose of ibrutinib to 280 mg once daily

The correct answer is: D (Reduce dose of ibrutinib to 280 mg once daily)

Answer rationale:

- The patient is currently responding well to ibrutinib and develops a cardiac arrhythmia that is able to be rate controlled with metoprolol.
- Since this is the patient's first cardiac event, continuing therapy with ibrutinib would be reasonable with a dose reduction and continued monitoring; particularly given that she is not requiring anticoagulation therapy.
- Changing therapy may be considered due to intolerance if there are further cardiac events or toxicities. Although second generation BTK inhibitors (such as acalabrutinib and zanubrutinib) may be associated with a lower risk of atrial fibrillation, in a patient with recurrent atrial fibrillation despite lowering the dose of ibrutinib, it would be prudent to consider switching classes of drugs entirely (to venetoclax and anti-CD20 monoclonal antibody). Additionally, it would be important to ensure that the patient still continues to meet indications for CLL directed therapy. In the E1912 study (frontline CLL therapy comparing ibrutinib-rituximab to FCR), patients who stopped ibrutinib due to toxicity did not require treatment for a median of 25 months after stopping ibrutinib.
- Hypertension risk with ibrutinib (and other BTK inhibitors) increases over time with prolonged use unlike some other BTK inhibitor-related adverse events which decrease over time.
- Pirtobrutinib is not appropriate as this patient has not progressed on a BTK inhibitor and a venetoclax-based regimen.

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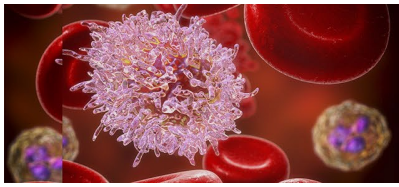

MUTATIONS, SEQUENCING, RESISTANCE: ADVANCES AND UPDATES IN CHRONIC LYMPHOCYTIC LEUKEMIA

Asymptomatic progression

Question 7

A 73-year-old man with a 4-year history of chronic lymphocytic leukemia is evaluated in follow-up. At diagnosis, cytogenetic analysis showed *IGHV* mutation, negative for TP53, and no del(17p). Therapy with zanubrutinib, 160 mg twice daily, was started, and has been well tolerated for 4 years without adverse events.

On examination, the patient feels well with normal energy and no adverse event. There is slight axillary lymphadenopathy and no organomegaly.

Laboratory evaluation shows:

Hemoglobin	12.5 g/dL
Leukocyte count and differential	18,000/µL with 75% lymphocytes
Platelet count	115,000/ µL
Serum creatinine	1.0 mg/dL

NGS study on the peripheral blood now shows the presence of C481S mutation.

Lymphocyte count is increased from previous tests.

Which one of the following is the most appropriate therapy for this patient at this time?

A. Continue zanubrutinib 160 mg twice daily
B. Switch to acalabrutinib 100 mg twice daily
C. Switch to pirtobrutinib 200 mg once daily
D. Switch to venetoclax once daily with dose ramp up to 400 mg plus rituximab 375 mg/m^2 IV

The correct answer is: A (Continue zanubrutinib 160 mg twice daily)

Answer rationale:

- Asymptomatic disease
- Despite NGS testing highlighting a resistance mutation with C481S, the appropriate treatment is to continue with zanubrutinib therapy.
- Continue to monitor patient and watch for symptomatic changes and disease markers for progression until the 2018 iwCLL guidelines are met for switching treatments.
- If patient does progress with symptomatic disease at a later time, then a venetoclax-based regimen would likely be the best option for second-line treatment.
- Pirtobrutinib is currently approved following 2 lines of therapy for CLL.
- In patients who develop progression of disease on a covalent BTK inhibitor (such as ibrutinib, acalabrutinib or zanubrutinib), switching to another covalent BTK inhibitor would not be expected to work. Therefore, in this patient treatment with acalabrutinib is not appropriate.

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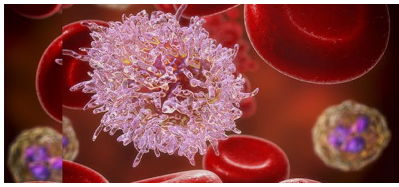

MUTATIONS, SEQUENCING, RESISTANCE: ADVANCES AND UPDATES IN CHRONIC LYMPHOCYTIC LEUKEMIA

Relapsed/Refractory CLL – Third line treatment

Question 8

A 68-year-old woman with a 6-year history of chronic lymphocytic leukemia is evaluated for progressive fatigue and bruising. Her medical history also includes hypertension and type 2 diabetes mellitus. The patient was originally treated with acalabrutinib and had a significant response; however, her disease progressed 1 year ago, at which time venetoclax plus obinutuzumab was prescribed. She is currently receiving venetoclax monotherapy.

On physical examination, lymphadenopathy is present and the spleen is palpable. Her performance status is good.

Laboratory evaluation shows:

Hemoglobin	9.3 g/dL
Leukocyte count with differential	55,000/µL with 78% lymphocytes
Platelet count	83,000/µL
Serum creatinine	1.1 mg/dL

Cytogenetic analysis shows *IGHV* unmutated, and TP53 mutation present.

Which one of the following therapies is most appropriate for this patient?

A. Bendamustine plus rituximab
B. Ibrutinib
C. Pirtobrutinib
D. Zanubrutinib

The correct answer is: C (Pirtobrutinib)

Answer rationale:

- Patient has progressed on 2nd generation BTK inhibitor (acalabrutinib) and BCL-2 inhibitor (venetoclax) based therapy
- Pirtobrutinib is a noncovalent BTK inhibitor and is currently FDA approved for relapsed/refractory CLL in patients who have had disease progression on 2 or more prior therapies including BTKi and BCL-2 inhibitor
- Pirtobrutinib has activity against the C481 mutation and is an appropriate 3rd line option for patients with high-risk disease (*IGHV* unmutated, TP53 mutation)
- Ibrutinib and zanubrutinib are not recommended after failure of a previous covalent BTK inhibitor. Chemoimmunotherapy would not be the best option for the patient at this time based on pirtobrutinib data (BRUIN trial) and NCCN guidelines

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Watch and wait phase/Survivorship considerations in CLL

Question 9

A 74-year-old male recently diagnosed with CLL based on peripheral blood flow cytometry done when incidental lymphocytosis was discovered during an annual physical examination is being evaluated for treatment. Additional evaluation shows mutated *IGHV* genes and del(17p) by FISH. Staging for disease is Rai 0 and Binet A.

Baseline laboratory data:

Hemoglobin	14 g/dL
Leukocyte count and differential	7,000/µL with 45% lymphocytes
Platelet count	150,000/µL
Serum creatinine	0.9 mg/dL
Uric acid	6.4 mg/dL

Which one of the following is the most appropriate management for this patient at this time?

A. Conduct age-appropriate cancer screening
B. Initiate allopurinol prophylaxis once daily
C. Initiate ibrutinib therapy
D. Initiate trimethoprim-sulfamethoxazole prophylaxis once daily

The correct answer is: A (Conduct age-appropriate cancer screenings)

Answer rationale:

- CLL12 study showed no survival benefit with ibrutinib in patients with early-stage high-risk asymptomatic CLL compared to placebo – hence the standard of care for patients who do not meet the 2018 iwCLL criteria for therapy remains "watch and wait," despite the presence of del(17p).
- Patients with CLL have a higher risk of developing secondary cancers, including melanoma and nonmelanoma skin cancers. Cancer screening and follow-up is especially important in patients with CLL. Annual dermatologic skin screening is recommended.
- Standard screening guidelines should also be closely followed for other secondary cancers such as breast, cervical, colon, and prostate cancers.
- Patients with CLL are at a higher risk for developing infections compared to the general population, even in the untreated stage – and should therefore receive appropriate immunizations according to the CDC guidelines for immunocompromised hosts.
- The patient is not at risk for TLS as he is not on active treatment and laboratory data are within normal ranges. Risk factors for TLS in patients with CLL include patients receiving venetoclax, lenalidomide, or obinutuzumab, bulky lymph nodes, elevated white blood cell count, renal disease, and pre-existing elevated uric acid.
- Since the patient is not on active therapy with a BTK inhibitor or other immunosuppressive chemotherapy regimen, the risk for opportunistic infections is low and the patient would not be appropriate for *Pneumocystis jiroveci* pneumonia (PJP) or other opportunistic infection prophylaxis

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