Oral Therapies in Lymphoma

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Warning!

This is NOT comprehensive and doesn’t apply to each situation

ALWAYS consult your treating oncologist regarding whether a therapy is appropriate for your specific case

Many oral therapies (included here and otherwise) are being investigated in clinical trials

Off label use of oral therapies MAY be appropriate for you but in consultation with your oncologist and in consideration of your case
Outline

• General considerations of lymphoma treatments
• Oral therapy myths
• General disease-specific indications and drug toxicities
• Talking points, questions to consider, and future directions
Management Options in Lymphoma/CLL

• Observation/ Watchful Waiting
• Chemotherapy (typically intravenous)
• Immunotherapies
  • Antibodies
  • Antibody-drug conjugates
  • Bi-specifics
  • CAR-T
• Radiation Therapy
• Radioimmunotherapy
• Oral Therapies
Pros / Cons of Oral Therapy (General)

Pros
• Convenience of administration
• No infusion center
• No port needed
• May have less severe toxicity
• May be more effective
• Continuously treating cancer

Cons
• Adherence can be difficult
• Cost & Hassle of obtaining
• Chronic low-grade toxicities
• Late, unexpected toxicities
• Chronic therapy
Common Oral Therapy Myths

1. Oral therapies are not “chemo” and are therefore less toxic

While toxicities may be different with oral therapies, they can still be severe and life threatening.
Common Oral Therapy Myths

Oral therapies are experimental and not proven

Some oral therapies are being evaluated in a clinical trial still but many others are FDA approved therapy options.
Common Oral Therapy Myths

Oral therapies are less effective than chemotherapy

Many oral therapies have actually proven to be MORE effective than traditional chemotherapy.
Common Oral Therapy Myths

Oral therapies are safer than chemotherapy and are not associated with risk of infection.

Several severe infections have been described and it is important to maintain close contact with your treating oncologist.
Common Oral Therapy Myths

Oral therapies are prohibitively expensive for most patients

Although expensive, almost all eligible patients are able to receive indicated therapy at a reasonable cost.

*Be sure to share concerns with oncologist.*
Types of Oral Therapies

• Conventional Chemotherapy
  • Chlorambucil (CLL)

• Immunomodulators
  • Lenalidomide (MCL, FL, others)

• Targeted Therapies
  • Bruton’s Tyrosine Kinase (BTK) inhibitors
    • Ibrutinib
    • Acalabrutinib
  • Phosphoinositide-3 kinase (PI3K) inhibitors
    • Idelalisib
    • Duvelisib
  • BCL2 Inhibitor
    • Venetoclax
  • Others
Is an Oral Therapy appropriate for me?

• Considerations of Oral Therapies (with or without other treatments)
  • CLL/SLL
  • Follicular lymphoma
  • Marginal Zone Lymphoma
  • Mantle Cell Lymphoma
  • Lymphoplasmacytic Lymphoma
  • Some Aggressive NHL’s including Diffuse large B-cell lymphoma

• Generally not outside clinical trial
  • Hodgkin lymphoma
  • Burkitt lymphoma
  • Peripheral T-cell lymphoma (some exceptions)
Chemo vs Ibrutinib in CLL

**Treatment-Naive CLL**
- N=523
  - CLL (IWCLL criteria)
  - CLL requiring treatment (IWCLL criteria)
  - Intermediate- or high-risk Rai stage

**Bendamustine + Rituximab (6 cycles)**

**Ibrutinib (QD)**

**Ibrutinib (QD) + Rituximab (6 cycles)**

**Ibrutinib (QD) + Rituximab (7 cycles)**

**Fludarabine + Cyclophosphamide + Rituximab (6 cycles)**

**Treatment-Naive CLL/SLL**
- N=529
  - CLL (IWCLL criteria), or SLL (WHO criteria)
  - Disease requiring treatment
  - Age ≤70 years
  - No deletion of 17p13
  - ECOG PS 0-2

Woyach et al, NEJM 2018; Shanafelt et al, NEJM 2019
Ibrutinib in Relapsed CLL

- Ibrutinib – 420mg once daily
  - Commonly used if not received already
  - Typically given “indefinitely”
  - Can be associated with high out of pocket cost

- Half of patients haven’t progressed at 4 years

Byrd et al, *Blood* 2019
Acalabrutinib in relapsed CLL

- Administered twice daily
- Not currently FDA approved for this indication

Byrd et al, NEJM 2016
Ibrutinib + Venetoclax in CLL/SLL

A Study Schema

B Response to Treatment over Time

Complete remission, with or without normal blood count recovery
Partial remission
Undetectable MRD in bone marrow

Jain et al, NEJM 2019
Toxicities of BTK Inhibitors

- Bleeding Bruising
- Fatigue
- Atrial Fibrillation (and other heart rhythm abnormalities)
- Infections
- Hypertension
- Joint Aches
- Diarrhea
- Rash
Toxicity of Venetoclax – Tumor Lysis Syndrome

• Tumor Lysis Syndrome
  • Potentially life threatening response to treatment
  • Leukemia cells die/break down and release intracellular contents
    • High uric acid
    • High potassium and other electrolyte abnormalities
    • Kidney damage
  • Managed/prevented with hydration and medication
• May require hospitalization to initiate therapy
• All patients complete a “ramp up” during the first month of treatment
Preventing and Managing TLS

• Drink large amounts of water prior to while on treatment
• Commonly will use an oral medication (Allopurinol)
• Frequent blood work during the first few weeks of treatment
• Be flexible with appointments/scheduling and expect frequent visits

• Good News: TLS primarily occurs during first few weeks and is typically fully reversible with no long term complications
• Early hassle gives way to long-term well-tolerated treatment
PI3K Inhibitors

- Several available
  - Idelalisib (oral)
  - Duvelisib (oral)
  - Copanlisib (Intravenous)

- Idelalisib combined with rituximab in CLL/SLL

- There is comparable efficacy and toxicities among these agents
PI3K toxicities – Rare but can be serious

• Infectious
  • CMV and Pneumocystis pneumonia (serious but rare infections)

• Immune-mediated
  • Colitis
  • Pneumonitis (Lung inflammation)
  • Liver toxicity
  • Rash

• Some agent-specific:
  • Hypertension
  • Hyperglycemia
**My CLL/SLL Approach – Integration of Oral Tx**

- **Prognostic Evaluation:** FISH and IGVH Mutation Status
  - IgHV Unmutated, del17p or del11q → Ibrutinib
  - IgHV Mutated AND no high risk cytogenetics → Assess Candidacy for Chemotherapy
  - ≤60 and candidate for chemotherapy → FCR (chemotherapy)
  - All Others

- **Considerations for Elderly/Infirm:**
  - Obinutuzumab/Venetoclax
  - Obinutuzumab/Chlormabucil

- **Consideration in patients who can’t/won’t adhere to chronic oral therapy:**
  - B-R (I rarely use this in untreated CLL)

- **Always consider clinical trial enrollment**
Combining Oral Agents in CLL

**EA9161**

- **Arm A**
  - **Ibrutinib**: Cycles 1-19: d1-d28 420mg PO daily
  - **Obinutzumab**:
    - Cycle 1: d1 100mg IV
d2 900mg IV
d8 1000mg IV
d15 1000mg IV
d1 1000mg IV
  - Cycles 2-6: d1 1000mg IV

- **Arm B**
  - **Ibrutinib**: Cycles 1-19: d1-d28 420mg PO daily
  - **Obinutzumab**: Cycles 1: d1 100mg IV
d2 900mg IV
d8 1000mg IV
d15 1000mg IV
  - Cycles 2-6: d1 1000mg IV

- **Venetoclax**:
  - Cycle 3: d1-d7 20mg PO daily
d8-d14 50mg PO daily
d15-d21 100mg PO daily
d22-d28 200mg PO daily
  - Cycles 4-14: d1-d28 400mg PO daily

- **Stratification**
  - Age: < 65 yrs vs. ≥ 65 yrs and ≥ 70 yrs
  - PS: 0, 1, vs. 2
  - Stage: 0, 1, or 2 vs. 3, 4
  - del11q22.3 (ATM) vs. other

- **Randomize**
  - **Acrual** = 720
  - **Cycle length** = 28 days

1. For patients on Arm B who complete 19 cycles of study treatment, ibrutinib should be continued at a rate of 420mg PO once daily under observation until disease progression.

- **18 months of therapy**
Oral Therapies in Follicular Lymphoma

- Rituximab – Lenalidomide
  - Untreated: Equivalent to chemotherapy (RELEVANCE)

Morschhauser et al NEJM 2019
Oral Therapies in Follicular Lymphoma

- Rituximab – Lenalidomide
- Relapsed/Refractory: Superior to Rituximab monotherapy

Leonard et al, J Clin Oncol 2019
Lenalidomide – Toxicities/Caution

• Thromboembolic disease
  • Typically requires anti-platelet or blood thinner

• Birth defects

• Fatigue

• Rash

• Low Blood Counts

• Commonly requires close monitoring and dose adjustments
PI3K Inhibitors Effective in Rel/Ref FL

- Idelalisib and Duvelisib are Oral Options in Rel/Ref FL
  - Copanlisib also (Intravenous)

- Subtle differences in toxicity – discuss with your oncologist

- Should NOT be utilized in untreated patients (with chemo)
FL progressing within 2 years or refractory to chemoimmunotherapy

Stratify:
- maintenance therapy
- lack of CR / early POD

Mandatory specimen submission

TGR-1202 + Obinutuzumab
N = 45

Lenalidomide + Obinutuzumab
N = 45

O-CHOP OR O-Bendamustine
N = 45

Primary clinical objective: CR by PET/CT
Primary translational objective: Validation of m7-FLIPI in this high-risk population
Mantle Cell Lymphoma

• Ibrutinib & Acalabrutinib approved in relapsed setting
• Venetoclax with promising efficacy
• Lenalidomide (typically with rituximab) in upfront and relapsed setting
• Promising Combinations
  • Ibrutinib/Venetoclax
  • Ibrutinib/Ixazomib
  • Ibrutinib/Palbociclib

• Generally – remissions not as durable as in CLL/SLL
• Several high profile studies should be reported soon
DLBCL – Caution!

• Oral Therapies less promising in DLBCL (in general)
  • Ibrutinib + RCHOP
  • Lenalidomide + RCHOP

• Both studies with caveats – likely subgroups of patients DO benefit

• Generally consider oral therapies on study in DLBCL
General Talking Points / Considerations

- It is critical to discuss the goals of any therapy prior to starting:
  - How will you know it is working?
  - When will you stop the treatment?
  - Does the requirements of the treatment fit with your goals/lifestyle?
General Talking Points / Considerations

• Oral therapy has changed our thoughts regarding toxicity

  Communicate with your team about ongoing side effects (even if minor)

  Some toxicities emerge later in the course

  We are still learning about some of the long term side effects
General Talking Points / Considerations

• More is not always better

  Two (or three) drugs may not improve overall outcome

  Consider goals of treatment and opportunity to discontinue therapy

  Sequential approach may be equivalent
General Talking Points / Considerations

• Communicate clearly with your team about costs

  Therapies must be taken regularly, on schedule

  We can almost always work out how to obtain therapy for reasonable cost
Future Directions

• Studies underway to evaluate time-limited treatment
• Chemotherapy + Oral Agents
• Molecular assessments may identify most appropriate treatment
• Consider enrolling in a clinical trial evaluating these exciting therapies
Thank you and Questions