New and Emerging Treatments in non-Hodgkin Lymphomas

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Outline

• Updates in DLBCL treatments
• Updates in MCL treatments
• Updates in FL treatments
NHLs come in many forms

- Indolent
  - Follicular, CLL/SLL
- Aggressive
  - DLBCL, mantle cell
- Highly aggressive
  - Burkitt

WHO Classification of Lymphoid Malignancies, 2016 update
Updates in DLBCL treatment – 1st line

• For >20 years, R-CHOP has been the standard treatment for DLBCL
  • Cures most patients (~65%) depending on stage and other factors
  • MANY attempts to improve upon R-CHOP results have failed
  • R-CHOP remains the standard for most people with DLBCL
    • More aggressive regimens are used for uncommon subtypes of DLBCL
      • Primary mediastinal B cell lymphoma
      • Double-hit lymphoma
Updates in DLBCL treatment – 1\textsuperscript{st} line, early stage

- Until recently, treatment of early stage (I,II) DLBCL was either with R-CHOP x 3 cycles and radiation or with R-CHOP x 6 cycles without radiation.

- 2 newer studies (FLYER and S1001) suggest very good outcomes without radiation treatments (which can have unwanted long-term effects).
  - FLYER – compared 6 cycles of R-CHOP to 4 cycles of R-CHOP and 2 cycles of rituximab. Very low-risk patients included. Outcomes were identical.
  - S1001 – PET-adapted approach. R-CHOP x 3 cycles followed by PET scan. Patients with negative PET scan (~85%) received a 4\textsuperscript{th} and final R-CHOP cycle. Patients with positive PET scan received radiation and radioimmunotherapy.

- Today, most people with early-stage DLBCL can receive 4 cycles of R-CHOP without the need for radiation therapy.
  - Exception might be people with larger (bulky) tumors.
Updates in DLBCL treatment – 1\textsuperscript{st} line, advanced stage

- R-CHOP x 6 cycles remains the standard for most

- Genentech press release: Phase III, randomized, placebo-controlled POLARIX trial met its primary endpoint
  - 879 patients with advanced stage DLBCL randomized to receive:
    - 6 cycles of R-CHOP and 2 doses of rituximab
    - 6 cycles of R-CHP + polatuzumab and 2 doses of rituximab

- Data are not yet published but will be presented to oncologists in December

- The POLARIX study results could change the standard treatment for people with advanced stage DLBCL for the first time in 20+ years!

Hamilton et al, Biologicals 2015
Updates in DLBCL treatment – relapsed/refractory

• For decades, standard treatment of relapsed or primary refractory DLBCL has been salvage chemotherapy followed by autologous stem cell transplantation
  • For younger, fitter people with chemosensitive disease, this approach cures ~20-40%

• Many people are not suitable for this approach (older, other health problems, lymphoma that does not go into remission after salvage treatments)
  • CAR T cell therapy may be an option for some (as third-line treatment)
  • Several new drugs or drug combinations have recently been FDA-approved
    • Polatuzumab + bendamustine + rituximab (pola-BR)
    • Tafasitamab + lenalidomide (tafa-len)
    • Loncastuximab tesirine (lonca)
    • Selinexor
Updates in DLBCL treatment – relapsed/refractory

Bruno et al, Hematologica 2021

Kochenderfer et al, Nat Rev Clin Oncol 2013
Updates in DLBCL treatment – relapsed/refractory

• For people with DLBCL that has relapsed after autologous stem cell transplantation or that has been resistant to 2 prior treatments, there are now 3 FDA-approved CAR T cell treatments
  • Axicabtagene Ciloleucel (Axi-cel; Yescarta; Kite/Gilead)
  • Tisagenlecleucel (Tisa-cel; Kymriah; Novartis)
  • Lisocabtagene Maraleucel (Lisa-cel; Breyanzi; BMS)

• All 3 CAR T cell products ”see” the identical target (CD19) on lymphoma cells

• Longer-term effectiveness seems to be similar; incidence of side-effects differs between products

• ~30-40% of people that receive CAR T cell therapy have long remissions and may be cured

• Figuring out the best treatments for those who relapse after CAR T cell therapy is an area of intense study
Updates in DLBCL treatment – relapsed/refractory

- CAR T cell therapy is currently approved for people with DLBCL that has relapsed after autologous stem cell transplantation or after 2 prior treatments.

- However, 2 recent clinical studies, ZUMA-7 and TRANSFORM, that tested CAR T cell therapy versus autologous stem cell transplantation as the first treatment for relapsed or refractory DLBCL have reportedly shown better effects of CAR T cell therapy based on recent press releases.
  - CAR T cell therapy may be used in the second line of treatment in lieu of salvage chemotherapy and autologous stem cell transplantation

- Many, many drugs and immunotherapies are being developed. I am happy to answer specific questions about any of these in the Q&A session.
Updates in MCL treatment – 1st line

• Mantle cell lymphoma (MCL) is typically an aggressive disease (not always though)

• First treatment in younger, fitter people is aggressive chemotherapy and rituximab followed by autologous stem cell transplantation and maintenance rituximab

• There is a very important clinical study ongoing across the country asking the question whether people who have had a VERY GOOD response to initial rituximab-chemotherapy actually NEED a stem cell transplant or can just go on to receive maintenance rituximab.

• For older, less fit people, initial treatment with bendamustine and rituximab, with or without cytarabine, is commonly used and is very effective.
Updates in MCL treatment – 2nd line and beyond

- Drugs called BTK inhibitors are very effective in relapsed MCL

- There are 3 BTK inhibitors approved – ibrutinib, acalabrutinib, zanubrutinib

- About 65-80% of people with relapsed MCL will respond well to these drugs
  - There is no obvious difference in effectiveness, but the newer BTK inhibitors (acalabrutinib and zanubrutinib) seem to cause less side effects
  - Major problem besides side effects is resistance

- CAR T cell therapy (brexucabtagene autoleucel; Tecartus; Kite/Gilead) was FDA-approved for people with MCL that was resistant to BTK inhibitors
  - Very high response rate
  - Treatment was associated with high incidence of typical CAR T side-effects
  - Durability of response following CAR T for MCL is still an open question

- Many other new drugs/therapies are being explored. Happy to answer ?s.
Updates in FL treatment – 1st line

- There are 2 (maybe 3) standard initial treatments for people with FL who NEED treatment
  - Bendamustine/rituximab (BR)
  - Lenalidomide/rituximab (R2)
  - R-CHOP

- The RELEVANCE study compared BR and RR in a randomized, phase III study and found equivalent efficacy but different side-effect profiles

- R-CHOP is used less commonly as initial FL treatment these days given its more pronounced side-effect profile and non-superior effectiveness

- Use of maintenance rituximab treatment remains controversial (prolongs remission duration and time to next treatment, but no overall survival benefit)

- Although remission durations with RR and BR are long (4-5 years), the lymphoma typically comes back
  - Still searching for a curative treatment for this and other indolent NHLs
Updates in FL treatment – 2nd line and beyond

• In the past 5 years, several studies have identified that a group of patients with FL (~20%) who relapse within 24 months of completing initial treatment (POD24) represent a high-risk group that may require new treatment approaches
  • Identifying these people and encouraging them to enroll on clinical studies is important toward improving treatment outcomes

• CAR T cell therapy with Axi-Cel has also been approved for FL (ZUMA-5) after 2 or more prior systemic treatments
  • Response rates are very high initially
  • Durability of responses induced by CAR T cell therapy remains to be seen
  • Very promising

• Tazemetostat (EZH2) inhibitor
  • Oral therapy; high response rates; reasonable response duration
  • Approved for patients with activating EZH2 mutated FL
  • Approved for patients with FL where no other standard treatment is available
Updates in FL treatment – 2nd line and beyond

• Many promising drugs/immunotherapies in development
  • Combinations including lenalidomide
  • Bispecific immunotherapy
  • CD47 blockade immunotherapy

• Happy to answer ?s