THE UNIVERSITY OF CHICAGO MEDICINE

Comprehensive Cancer Center

UC Cancer Research Foundation

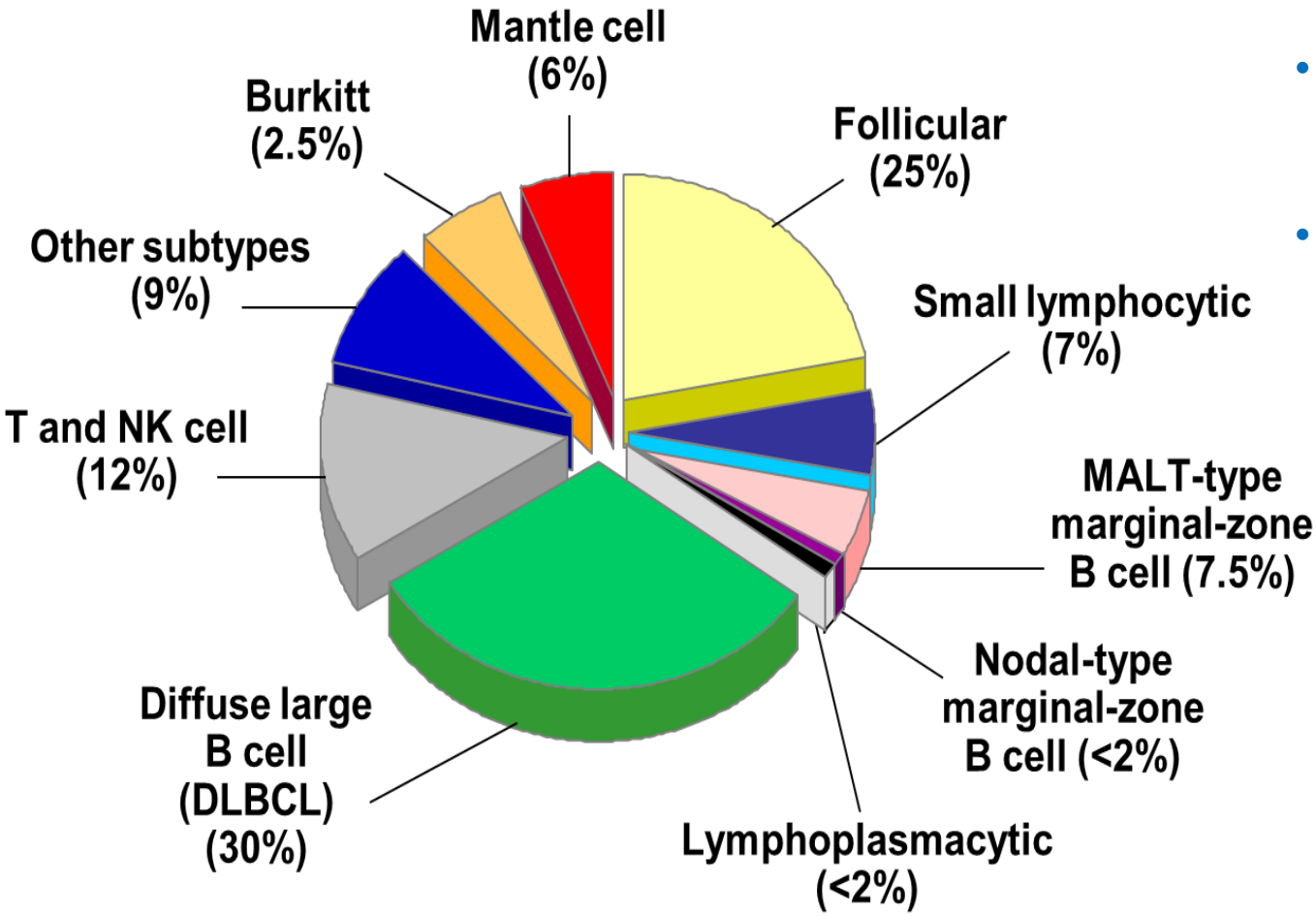
New and Emerging Treatments in non-Hodgkin Lymphomas

Justin Kline, M.D.
Associate Professor, Department of Medicine
Director, Lymphoma Program
Committees on Immunology and Cancer Biology
University of Chicago Comprehensive Cancer Center

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 – 1st 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.

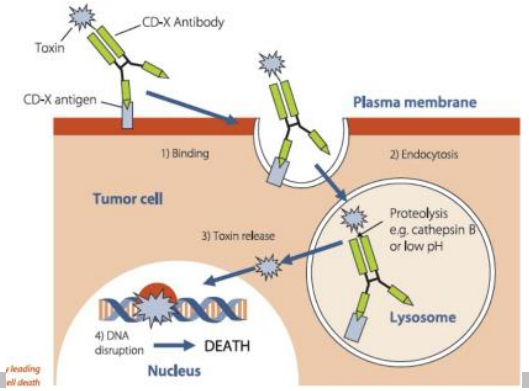
    - S1001 – PET-adapted approach. R-CHOP x 3 cycles followed by PET scan. Patients with negative PET scan (~85%) received a 4th and final R-CHOP cycle. Patients with positive PET scan received radiation and radioimmunotherapy.

- 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 – 1st 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!



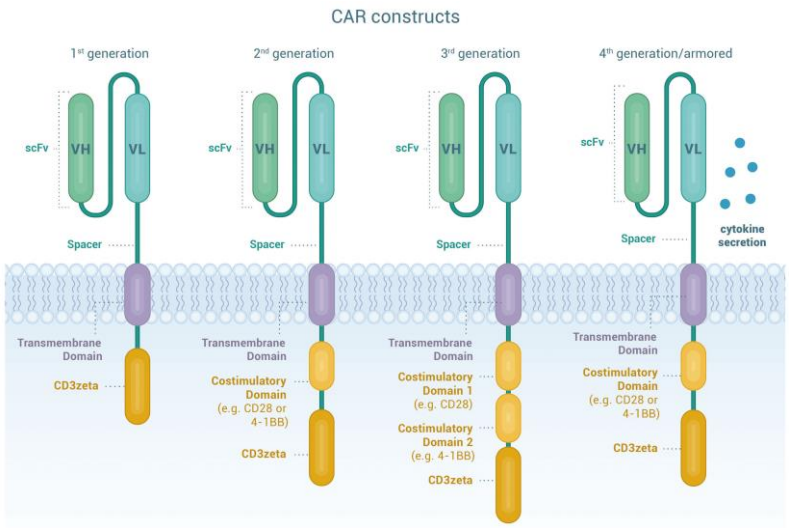
Hamilton et al, Biologicals 2015

Updates in DLBCL treatment – relapsed/refractory

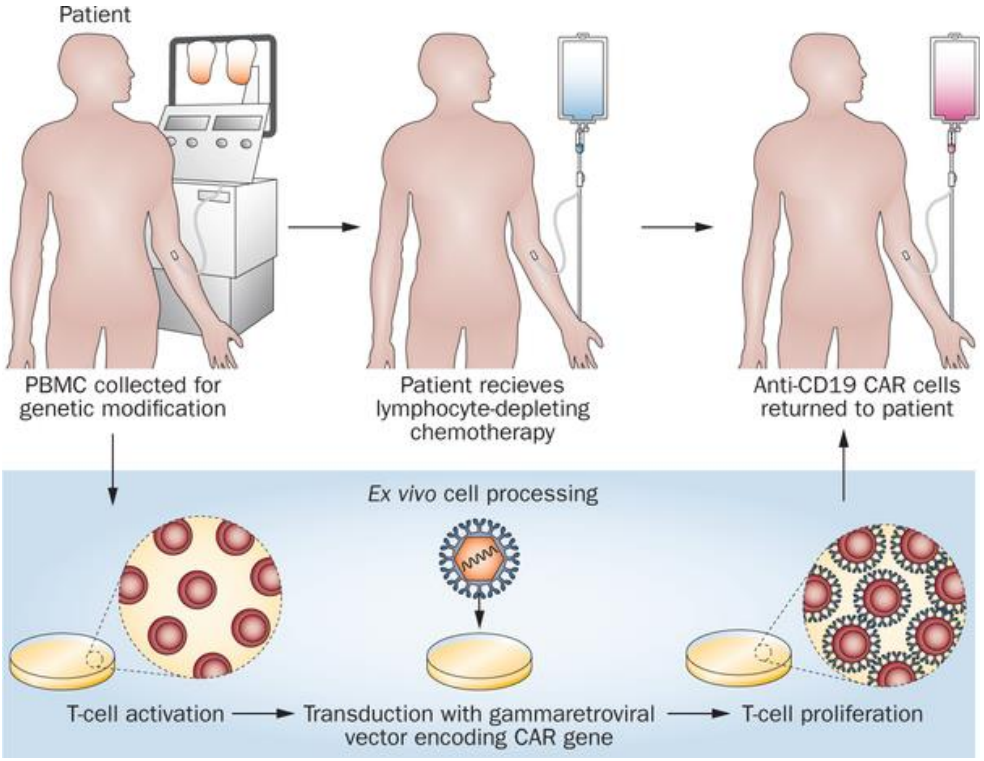
- For decades, standard treatment of relapsed or primary refractory DLBCL has been salvage chemotherapy followed by autologous stem cell transplantation
  - For younger, fitter people with chemosensitive disease, this approach cures ~20-40%

- 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