Which is the best immune approach to replace ASCT?

CAR-T?

PARAMESWARAN HARI
PROFESSOR AND CHIEF ; DIVISION OF HEMATOLOGY ONCOLOGY
MEDICAL COLLEGE OF WISCONSIN
DISCLOSURES

• Honoraria & Consulting:
  • BMS / Janssen / Takeda / Amgen / GSK
  • Karyopharm
  • Kadmon
  • Kite/ Gilead

Major disclosure – CARD CARRYING TRANSPLANTER
Questions to consider

• CAR-T or bispecific – which modality is likely to win?
• Transplant based Upfront Therapy in MM:
  • What’s standard expectation in 2021?
  • Will improved induction and maintenance with ASCT move the goal post further?
• How do we know what is a win for CAR-T vs. ASCT?
  • MRD Assessment?
  • What should a trial look like?

CAVEAT:
All forward looking statements.....
No real comparative data
Benefits of Upfront ASCT ..... 

• Most reliable way to an early MRD neg CR
• Longest upfront PFS or PFS1 among current options
• A minority may never need any further therapy – Cure Fraction
• Long period free of intense therapy or any therapy
• Low Non-relapse mortality (NRM) - ~0.5% in RW studies
• Safe in elderly, dialysis dependent
• As Induction/maint improves – outcomes improve for the “ASCT package”
• World-wide access - arguably better than many drugs in MM
## Front Runner CAR-Ts in RRMM

<table>
<thead>
<tr>
<th></th>
<th>KarMMa</th>
<th>Ciltacel</th>
<th>Orvacel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med /Max Age</td>
<td>61/78</td>
<td>61/78</td>
<td>61/77</td>
</tr>
<tr>
<td>Median Prior</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Bridging</td>
<td>88</td>
<td>73</td>
<td>63</td>
</tr>
<tr>
<td>ORR</td>
<td>81%</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>CR/sCR</td>
<td>33%</td>
<td>67%</td>
<td>63%</td>
</tr>
<tr>
<td>MRD- in evaluable</td>
<td>94%</td>
<td>93%</td>
<td>84%</td>
</tr>
<tr>
<td>PFS / DoR</td>
<td>10.7</td>
<td>22.8/NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Main Messages:**

Best single agent CR/ MRD/ ORR rates and PFS in RRMM

**Non-curative modality .. At least in the RRMM setting**

NRM : is not trivial (albeit in RR-MM population)

**Idecel** : 17 deaths unrelated to PD (N-140). 3 died within 8 weeks & 1 - 8 weeks – 6 mo. (Aspergillosis, GI Bleed, CRS, late onset CMV)

**Ciltacel**: 9 deaths from non-PD related causes (N-113). *Sepsis/CRS/HLPneumonia/ AML*

<table>
<thead>
<tr>
<th></th>
<th>Ide-cel</th>
<th>Ciltacel</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>73%</td>
<td>97%</td>
</tr>
<tr>
<td>CR</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>MRD-, %</td>
<td>39%</td>
<td>54.6%</td>
</tr>
<tr>
<td>mPFS (all)</td>
<td>12.1*</td>
<td>23 mo</td>
</tr>
<tr>
<td>PFS in sCR</td>
<td>20.2*</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>CAR-T (current data)</th>
<th>Bispecific BCMA Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early MRD neg CR</td>
<td>REF</td>
<td>Better than ASCT</td>
<td>About the same as ASCT?</td>
</tr>
<tr>
<td>Disease free/ Rx free mo</td>
<td>~60 mo</td>
<td>Better if upfront?</td>
<td>Unknown? BUT need Rx</td>
</tr>
<tr>
<td>Cure fraction?</td>
<td></td>
<td>Possible? Better than ASCT?</td>
<td>No idea; NEED continuous RX</td>
</tr>
<tr>
<td>Hypogamma/ Immune Status</td>
<td>Reconst.</td>
<td>Worse than ASCT but improves?</td>
<td>Ongoing issue; late hypogamma</td>
</tr>
<tr>
<td>Access to center</td>
<td>World wide</td>
<td>Manufacturer accredited</td>
<td>Easiest; off the shelf</td>
</tr>
<tr>
<td>NRM</td>
<td></td>
<td></td>
<td>Low /Late Infection risk?</td>
</tr>
<tr>
<td>Safety – Age/comorbid</td>
<td></td>
<td></td>
<td>Safest</td>
</tr>
<tr>
<td>Effect on Cytogenetic HR</td>
<td></td>
<td></td>
<td>Better than ASCT?</td>
</tr>
<tr>
<td>PFS</td>
<td>60 plus mo</td>
<td></td>
<td>UNKNOWN UNKNOWN</td>
</tr>
<tr>
<td>Targets &amp; Innovation</td>
<td>None</td>
<td>BCMA + ...</td>
<td>BCMA/GPRC5D/FCRH5</td>
</tr>
</tbody>
</table>

Teclistamab in RRMM:
- 17 deaths unrelated to MM PD among 157 pts
- Pneumonia/ Sepsis / Covid-19/ Gen deterioration
- Profile of persistent hypogamma with rpt dosing
  - G≥3 infections in 45% of RP2D dosed pts

Usmani S et al Lancet 2021; Aug 10
Mechanisms of failure with CAR-T...

Will these be addressed by earlier use of CAR-T?
T cell phenotype?
Less clonally advanced MM responds better?

Hope of a cure with CAR-T... but
YES: T cells can mediate a cure – e.g. Allo HCT survivors; DLI
However – immune synapse is different
No active adaptation with CAR-T or bsAb
One modality may not cure

Gazeau N et al Effective anti-BCMA retreatment in multiple myeloma, Blood Adv, 2021
Earlier use of CAR-T leads to better PFS – can we assume?

**LEGEND data from Chinese Study vs. CARTITUDE 1**

<table>
<thead>
<tr>
<th>Time from initial MM diagnosis, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Number of prior lines of therapy, n</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
</tbody>
</table>

**Prior therapies, n (%)**

- Proteasome inhibitors: 39 (68)
- Immunomodulatory agents: 49 (86)
- Lenalidomide: 25 (44)
- Pomalidomide: 2 (4)
- Thalidomide: 39 (68)
- PI + IMIDs: 34 (60)

**CARTITUDE-2 cohort A, Median 2 lines of prior therapy**

ORR and MRD neg rates similar to CARTITUDE-1 at early time points

- ORR – 88%
- CR – 63%
- MRD Neg – 68%

**Median PFS – 15 mo**


PFS will be better for single agent CAR-T consolidn post induction – Are we sure?
CAR-T vs. ASCT ... What can lymphoma teach us?

• ZUMA-7 trial recently reported as “win” for CAR-T over ASCT in DLBCL

Phase 3 ZUMA-7: Axicabtagene Ciloleucel vs SOC (ASCT) in R/R DLBCL

- Phase 3, randomized, multicenter trial
- R/R DLBCL <12 mo from initiation of therapy
- Eligible for ASCT
  N = 359
- Primary endpoint: EFS

An MRD based study is easy to perform for upfront CAR-T in MM too ...

Unlike in DLBLCL:
  - Neither modality is truly curative
  - After induction very few pts will progress early and both groups will likely make it to CAR-T & ASCT
  - PFS / EFS will be defined by early relapsers who benefit from disease control in CAR-T arm i.e. HR-MM

So ... should we limit a MM study to HR-MM only?
NOVEL AGENTS HAVE NOT ELIMINATED TRANSPLANT SO FAR .. WILL CAR-T DO IT?

**Resounding win so far for transplant – higher PFS/ RR/ MRD neg rates**
(DETERMINATION II yet to read out)

**Induction** → **Stem Cell Harvest**

- Transplant (Hi dose MEL) x 1 or 2
- CAR-T therapy as non-transplant consolidation
- Similar Maintenance
- CAR-T at Relapse
- Transplant at Relapse

**This design can answer the PFS qn for CAR-T replacing UPFRONT ASCT**
But is that the right question for a million dollar therapy?
Sequencing ASCT-CAR-T or CAR-T-ASCT?
Reserve upfront CAR-T for pts predicted to NOT benefit from ASCT?

Even this design cannot answer
utility qn of CAR-T replacing ASCT
sequencing qn .... needs OS
**ASCT- PFS– MRD in current era**

Samur et al JCO 2020

DFCI/IFM trial

**G**

- ASCT helps PFS even in extremely good risk pts
- ASCT improves MRD Neg Rates even with good induction
- Even with MRD neg post ASCT – maintenance helps
- New Induction + ASCT + consolidation – limited upward MRD room
- HR & UHR pts with MRD neg still do poorly vs. SR-MM

---

**UK MRC XI data – de Tute et al IMW 2021**

<table>
<thead>
<tr>
<th></th>
<th>ASCT+3 PFS</th>
<th>ASCT+9 PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
</tr>
<tr>
<td>MRD (-ve vs +ve)</td>
<td>0.401</td>
<td>0.271-0.592</td>
</tr>
<tr>
<td>Treatment (len vs obs)</td>
<td>0.388</td>
<td>0.268-0.561</td>
</tr>
<tr>
<td>Cytogenetics (UHir+HR vs SR)</td>
<td>2.576</td>
<td>1.770-3.748</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ASCT+3 OS</th>
<th>ASCT+9 OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD (-ve vs +ve)</td>
<td>0.457</td>
<td>0.246-0.849</td>
</tr>
<tr>
<td>Treatment (len vs obs)</td>
<td>0.528</td>
<td>0.297-0.938</td>
</tr>
<tr>
<td>Cytogenetics (UHir+HR vs SR)</td>
<td>4.286</td>
<td>2.272-8.086</td>
</tr>
</tbody>
</table>

**DKRD induction**

- ASCT helps PFS even in extremely good risk pts
- ASCT improves MRD Neg Rates even with good induction
- Even with MRD neg post ASCT – maintenance helps
- New Induction + ASCT + consolidation – limited upward MRD room
- HR & UHR pts with MRD neg still do poorly vs. SR-MM

Costa L et al ASH 2019
UPFRONT CAR-T projects

Industry led projects

Practical Issues:
SYNERGISTIC or Mutually exclusive?

CAR-T after ASCT –
MRD convert those pos after ASCT &
Cure for SR-MM patients?

CAR-T before ASCT – wipe out persistence?

CAR-T using ASCT as a lymphodepleting tool?

Can we assess treatment discontinuation after 2 cell therapy modalities?

---

CTN 1901 Study Schema – HR-MM concept

CTN 1902 Study Schema – Response upgrade concept
BMT CTN State of the Science
MM concept

- HR and U HR disease ONLY

CONTROL POPULATION:
RVD-Dara x 4 → ASCT → RVd maintenance per Emory protocol
CAR-T BsAb & ASCT & some points to ponder

- CAR-T: Durable MRD Neg remissions (in RRMM setting)
  - Best option to replace/work with ASCT to get long upfront remissions
  - Best option for limiting therapy and increasing cure fraction without excess treatment
- Manufacturing issues & slot availability in addition to cost
- Affordability: a 10X cost increase for all MM pts?
- Competing therapies or Synergistic:
  - PBSC Collection after CAR-T possible?
  - Second CAR-T of the same kind does not usually work
- For now - I will still collect & store PBSC in every TE pt
- Equipoise on CAR-T vs. ASCT trials with crossover
- Outcome of ASCT after CAR-T or BsAb - big unknown
- Sustained use BsAb worry about immune reconstitution
- What got us here: Synergistic/Additive use of all modalities:
  - Need trials of early CAR-T (before/instead of and after ASCT)
  - Goal sus-MRD & Rx discontinuation
  - Cautious Optimism that BCMA CAR-T will do this
The reports of my death have been greatly exaggerated.