Immunotherapy Sequencing in Relapsed/Refractory Multiple Myeloma

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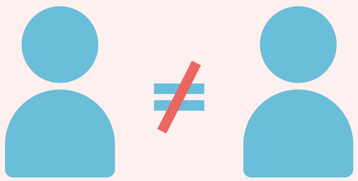
Introduction

Most patients with multiple myeloma undergo several cycles of remission and relapse during their disease journey, and multiple lines of therapy may be needed.[1]

However, the treatment landscape of relapsed/refractory multiple myeloma has evolved to include novel options.[1]

Selecting and sequencing effective treatment options requires consideration of resistance status to specific drug classes, as well as factors such as patient frailty, comorbidities, and preferences.[1] Outcomes may vary between individual patients.



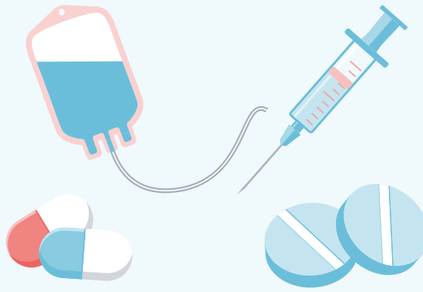
Optimising the Sequential Use of T-cell Redirecting Therapies

? With the availability of novel therapies, such as CAR T-cells and bispecific antibodies targeting BCMA and GPRC5D, what are the consensus recommendations for optimal sequencing?

Triplet therapy[1]

- From 1L+
- E.g., 2 classes of drug from PI, IMiD, and anti-CD38 mAb, plus dexamethasone
- Provided that the patient is able to tolerate it (those with poor PS or frailty may start on a two-drug regimen)
- Triplet therapy may include a drug from the anti-SLAM7 or SINE therapy classes from 2L onwards
- Alternative combinations can be used in subsequent lines, or the same combination as that used for primary therapy can be repeated if the relapse period if sufficiently long enough after the end of primary treatment

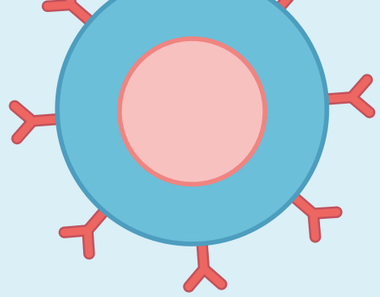
- Avoid high-dose alkylators and bendamustine in patients for whom next therapy is likely to be a planned CAR-T or BsAb[2]



CAR-T therapy[2-6]

- From first relapse: anti-BCMA CAR-T[3,4]
- Refer to CAR-T centre to assess eligibility

- Bridging therapy should be used to manage disease and stabilize the patient while the CAR-T cells are being manufactured; effective bridging therapy can optimize conditions for CAR-T therapy, potentially improving efficacy and patient outcomes
- BsAb may be a suitable bridging option prior to CAR T, ideally with a different immunological target
- A washout of 2 weeks is recommended prior to apheresis of mononuclear cells for CAR T-cell manufacturing
- Avoid collecting mononuclear cells for CAR T-cell manufacturing in patients receiving BsAb



BsAb therapy[7-12]

- From 4L+ (among other requirements)
- Indicated in patients exposed to PI, IMiD, and anti-CD38 mAb

- Patients with rapidly progressing disease may consider BsAb before CAR-T therapy due to faster access[2]
- BsAb depletes T cells, which may affect subsequent therapy[13]
- A washout of 2 weeks is recommended prior to the first dose of BsAb[2]

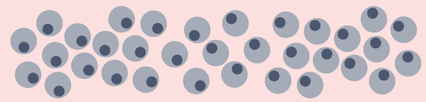
Direct comparison between different therapeutic drugs is not intended and should not be inferred in the absence of head-to-head prospective studies.

Reasons for considering CAR-T therapy before BsAb therapy:

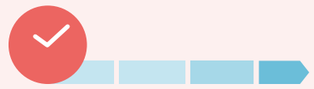
- BsAb can be effective after CAR-T, despite some attenuation of responses[2,14,15]
- CAR-T response may be suboptimal in patients exposed to prior BCMA-targeting BsAb[2,15]

Reasons for considering CAR-T before exhausting triple therapy options:[16]

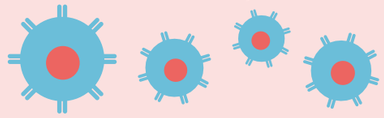
Bulky disease in later lines may reduce CAR-T efficacy



Potential for long-term remissions in earlier lines



Better T cell fitness and viability in earlier lines

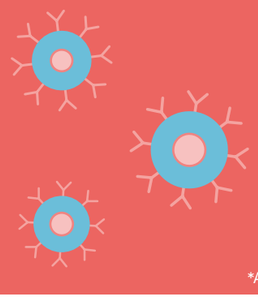


Better patient performance status earlier in the disease course

Key Learnings

Start planning for CAR-T as soon as a patient experiences a relapse after treatment; early planning increases the chances of securing a CAR-T slot and achieving better outcomes for patients.[13,15,17]

- **CAR-T therapy should be considered before BsAb therapy.[2,16,*]**
- **There is more robust data to support BsAb use after CAR-T therapy, and the potentially long treatment-free period after CAR-T therapy may allow for more salvage options upon disease progression.[2]**



There are limited data on the feasibility and efficacy of anti-BCMA CAR-T therapy upon progression on anti-BCMA BsAb; therapy with a different mechanism of action or immunotherapy targeting a different antigen is recommended in this scenario.[2]

*Assuming equal access, in patients who are eligible for both therapies

Abbreviations:

1L: first-line; 2L: second-line; 4L: fourth-line; BCMA: B cell maturation antigen; BsAb: bispecific antibody; CD: cluster of differentiation; GPRC5D: G protein-coupled receptor, class C, group 5, member D; IMiD: immunomodulatory imide drug; mAb: monoclonal antibody; PI: proteasome inhibitor; PS: Eastern Cooperative Oncology Group Performance Status; SINE: selective inhibitor of nuclear transport; SLAMF7: self-ligand receptor of the signalling lymphocytic activation molecule (SLAM) family.

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