CLINICAL FLASHCARDS

Moving CAR-T To Earlier Myeloma Lines

The Life Science Feed

QUESTION

In clinical haematology, what is the primary characteristic of multiple myeloma?

ANSWER

A cancer of plasma cells found in the bone marrow.

QUESTION

What three classes of drugs typically constitute the 'triplet' or 'quadruplet' therapy for first-line multiple myeloma?

ANSWER

A proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and dexamethasone (with or without an anti-CD38 antibody).

QUESTION

Term: Triple-refractory multiple myeloma

ANSWER

Definition: Myeloma that is refractory to a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody.

QUESTION

What was the historical median overall survival for patients with triple-refractory multiple myeloma prior to the advent of newer immunotherapies?

ANSWER

Approximately 13 months.

QUESTION

What does the abbreviation BCMA represent in the context of myeloma therapy?

ANSWER

B cell maturation antigen.

QUESTION

On which specific cell types is BCMA expression restricted in normal human tissue?

ANSWER

Normal plasma cells and some memory B cells.

QUESTION

Why does targeting BCMA allow for the potential of immune reconstitution after therapy?

ANSWER

BCMA is not expressed on haematopoietic stem cells.

QUESTION

Which two ligands signal through BCMA to promote the survival and proliferation of plasma cells?

ANSWER

APRIL and BAFF ligands.

QUESTION

What is the generic name for the first approved BCMA-directed CAR-T therapy, marketed as Abecma?

ANSWER

Idecabtagene vicleucel (ide-cel).

QUESTION

What is the generic name for the BCMA-directed CAR-T therapy marketed as Carvykti?

ANSWER

Ciltacabtagene autoleucel (cilta-cel).

QUESTION

Which clinical trial led to the approval of idecabtagene vicleucel in triple-class refractory myeloma?

ANSWER

The KarMMa trial.

QUESTION

According to the KarMMa trial, what was the median progression-free survival for ide-cel in triple-class refractory myeloma?

ANSWER

8.8 months.

QUESTION

What was the overall response rate (ORR) observed in the KarMMa trial for ide-cel?

ANSWER

73%.

QUESTION

What unique structural feature of cilta-cel distinguishes it from traditional scFv-based CAR-T constructs?

ANSWER

A dual-domain nanobody design with two antigen-binding domains.

QUESTION

What was the reported overall response rate (ORR) for cilta-cel in the CARTITUDE-1 trial?

ANSWER

97%.

QUESTION

In the CARTITUDE-1 trial, what percentage of patients achieved a complete response (CR)?

ANSWER

67%.

QUESTION

At the 27-month follow-up of CARTITUDE-1, what percentage of patients remained progression-free?

ANSWER

74%.

QUESTION

Which clinical trial compared cilta-cel against standard-of-care regimens in lenalidomide-refractory myeloma?

ANSWER

The CARTITUDE-4 trial.

QUESTION

What reduction in the risk of progression or death was demonstrated by cilta-cel in the CARTITUDE-4 trial?

ANSWER

74%.

QUESTION

The FDA recently approved cilta-cel for use as early as the _____ line of treatment.

ANSWER

Second

QUESTION

Term: GPRC5D

ANSWER

Definition: A G protein-coupled receptor expressed on myeloma cells used as an alternative CAR-T and bispecific target.

QUESTION

Apart from plasma cells, where is the expression of GPRC5D notably found in the body?

ANSWER

Hair follicles.

QUESTION

Which bispecific antibody targets GPRC5D and was evaluated in the MonumenTAL-1 trial?

ANSWER

Talquetamab.

QUESTION

What overall response rate (ORR) did talquetamab show in patients who had received a median of five prior lines of therapy?

ANSWER

73%.

QUESTION

Term: FcRH5

ANSWER

Definition: Fc receptor homolog 5, a target expressed on myeloma cells for therapies like cevostamab.

QUESTION

Which bispecific antibody is currently being developed to target FcRH5 in myeloma?

ANSWER

Cevostamab.

QUESTION

In the context of myeloma relapse after CAR-T, what does 'antigen escape' refer to?

ANSWER

The downregulation or loss of the target antigen, such as BCMA, on the cancer cells.

QUESTION

Beyond antigen escape, name a T-cell specific mechanism that contributes to CAR-T therapy failure.

ANSWER

T cell exhaustion (loss of effector function).

QUESTION

How does the tumour microenvironment contribute to CAR-T resistance in myeloma?

ANSWER

By creating an immunosuppressive environment that dampens CAR-T cell function.

QUESTION

What clinical strategy is emerging to address the problem of BCMA downregulation after initial CAR-T therapy?

ANSWER

Sequential targeting (e.g., following BCMA therapy with GPRC5D or FcRH5 targeted therapy).

QUESTION

Why is it generally recommended to collect T cells earlier in the course of myeloma treatment?

ANSWER

To avoid using T cells that have been damaged or depleted by heavy prior lines of therapy.

QUESTION

What is the typical manufacturing duration required to produce CAR-T cells for a patient?

ANSWER

2 to 5 weeks.

QUESTION

What are the two primary toxicities haematologists must manage following CAR-T infusion?

ANSWER

Cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS).

QUESTION

According to current debates in the field, which standard procedure is CAR-T therapy beginning to challenge in early-line treatment?

ANSWER

Autologous stem cell transplant (ASCT).

QUESTION

Which ligand, along with BAFF, is a primary driver of BCMA-mediated plasma cell survival?

ANSWER

APRIL.

QUESTION

The CARTITUDE-4 trial focused specifically on patients who were refractory to which immunomodulatory drug?

ANSWER

Lenalidomide.

QUESTION

Identify one proteasome inhibitor commonly used in the 'triplet' therapy for myeloma.

ANSWER

Bortezomib (or carfilzomib).

QUESTION

What is the primary goal of the 'bridging therapy' administered during CAR-T production?

ANSWER

To maintain disease control while the CAR-T cells are being manufactured.

QUESTION

What percentage of myeloma plasma cells typically express BCMA?

ANSWER

Over 90%.

QUESTION

Which GPRC5D-directed bispecific antibody was tested in the MonumenTAL-1 trial?

ANSWER

Talquetamab.

QUESTION

In the KarMMa trial, what percentage of patients achieved a complete response (CR) with ide-cel?

ANSWER

33%.

QUESTION

How does the dual-domain design of cilta-cel theoretically improve its efficacy compared to single-domain constructs?

ANSWER

By increasing the avidity and binding strength to the BCMA target.

QUESTION

Identify two emerging non-BCMA targets in the myeloma pipeline besides GPRC5D.

ANSWER

FcRH5 and SLAMF7 (or ROR1).

QUESTION

Which trial demonstrated a 97% overall response rate in triple-class refractory myeloma?

ANSWER

The CARTITUDE-1 trial.

QUESTION

What is the clinical significance of BCMA being a 'functional node' in myeloma biology?

ANSWER

Targeting it inhibits pathways essential for the cell's survival, not just its surface markers.

QUESTION

What is the main advantage of the sequential targeting paradigm in relapsed myeloma?

ANSWER

It provides therapeutic options for patients who have relapsed via antigen escape (BCMA loss).

QUESTION

Which drug is often added to the PI/IMiD/Dex triplet to form a quadruplet first-line therapy?

ANSWER

Daratumumab.

QUESTION

In terms of T-cell quality, what is a potential consequence of 'heavy prior therapy' before CAR-T collection?

ANSWER

Poor CAR-T cell expansion and persistence.

QUESTION

The RedirecTT-1 trial explored therapies targeting which specific antigen?

ANSWER

GPRC5D.

QUESTION

What specific type of B cell, other than plasma cells, may express BCMA?

ANSWER

Memory B cells.

QUESTION

Which BCMA CAR-T was the first to receive regulatory approval?

ANSWER

Idecabtagene vicleucel (Abecma).

QUESTION

Name one anti-CD38 antibody used in subsequent lines of myeloma treatment mentioned in the text.

ANSWER

Isatuximab.

QUESTION

What does the term 'ORR' stand for in oncology clinical trials?

ANSWER

Overall response rate.

QUESTION

In the context of CARTITUDE-4, what was the 'physician's choice' used as a comparator?

ANSWER

Standard-of-care regimens.

QUESTION

What is the name of the FcRH5-directed bispecific antibody discussed in the text?

ANSWER

Cevostamab.