Management of Hypogammaglobulinaemia and B-Cell Aplasia

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The development and regulatory approval of CAR-T cell therapies targeting B-lineage surface antigens (Maude et al. 2018), such as CD19 or CD22, represents a major milestone in cancer immunotherapy. This treatment results in the depletion of malignant and normal B cells and is associated with hypogammaglobulinaemia. These on-target, off-tumour toxicities may result in an increased risk of infection. Careful long-term follow-up assessment of patients receiving CAR-T cell therapy is important. Management of these on-target, off-tumour effects should be well coordinated between treatment and referring centres if the patient returns to local providers following therapy. Aims of this toxicity management:

- Prophylaxis of acute and chronic infections.
- Treatment of infections.
- Prevention of organ damage due to silent and/or chronic infections (e.g., bronchiectasis).
- Best-possible quality of life.

Monitoring B-cell aplasia provides information on two aspects of treatment. First, B-cell aplasia is a sign of functional CAR persistence and often shows longer persistence than direct detection of the CAR-T cells themselves. Monitoring B-cell aplasia can guide decisions on the interval of monitoring of the malignant disease (e.g., imaging, MRD) and subsequent allogeneic HSCT in cases of CAR-T cell failure. Therefore, B-cell aplasia should be monitored together with remission

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status and CAR persistence. Second, B-cell aplasia is a helpful parameter to guide tapering or continuation of IgG substitution. The evidence level for the recommendation concerning monitoring B-cell aplasia is based on expert opinion and may vary in different patient age groups.

Because anti-CD19 and anti-CD22 CAR-T cells attack B-lineage precursors, long-term hypogammaglobulinaemia or agammaglobulinaemia are commonly seen in patients after CAR-T cell treatment. In paediatric centres, it has been the standard of care to perform immunoglobulin replacement following CAR-T cell therapy (Maude et al. 2014). However, there is no consensus regarding systematic IgG supplementation in adults with plasma-cell aplasia and hypogammaglobulinaemia after CAR-T cell therapy. Since persistent B-cell aplasia is associated with sinopulmonary infections, notably with encapsulated bacteria (Fishman et al. 2019), intravenous immunoglobulin replacement is performed in all patients with hypogammaglobulinaemia plus recurrent or chronic infections, especially pneumonia. After allogeneic HSCT plus CAR-T cell therapy, patients face an increased risk of infection-related morbidity and hence may require intensified (perhaps lifelong) IgG substitution regimens.

The duration of IgG substitution may be lifelong or last at least until recovery of functional B cells and plasma cells. However, data regarding the efficacy of prophylactic IgG replacement in CAR-T cell therapy recipients are limited (Hill et al. 2019), and current expert recommendations (Mahadeo et al. 2019, Yakoub-Agha et al. 2020) are extrapolated from the data for individuals with primary immune deficiencies (Perez et al. 2017, Picard et al. 2018). The long-term follow-up data from patients with Bruton agammaglobulinaemia provide a rationale to closely monitor immunoglobulin levels and acute, chronic and especially silent infections to prevent organ damage and maintain long-term quality of life. Individualized regimens aim to maintain serum immunoglobulin levels above 400 µg/l in adults and age-adapted normal ranges for children. Intravenous immunoglobulins (IVIGs) are usually given every 3–6 weeks or subcutaneously weekly (SCIGs). IVIG doses start at 0.4 g/kg body weight and SCIG doses at 0.1–0.15 g/kg body weight. Doses and intervals are adapted due to infections and serum IgG levels. After reaching a steady state, serum IgG levels should be controlled at least every 3 months.

Studies are needed to establish evidence-based approaches for management of B-cell aplasia and hypogammaglobulinaemia. Prophylactic immunoglobulin administration in this context and strategies may differ by patient and CAR-T cell product characteristics.

Key Points

- Long-term (potentially lifelong) monitoring of B-cell aplasia and IgG levels is necessary after CD19/CD22 targeting CAR-T cell therapies.
- Maintain serum immunoglobulin levels at physiologic levels through regular intravenous or subcutaneous substitution.
- The evidence level of this recommendation is at the expert opinion level.

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