Mantle Cell Lymphoma

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Mantle cell lymphoma is a distinct lymphoma subtype with a widely varying clinical course. Established high-risk biological factors include blastoid cytomorphology, high cell proliferation (Ki-67 > 67%), and *p53* mutations (Aukema et al. 2018). While current first-line approaches are still chemotherapy-based, BTK inhibitors are the preferred targeted approach, especially in early relapse cases (POD24) (Dreyling et al. 2017; Visco et al. 2021). However, cases of relapse/progression under BTK inhibitors display extremely aggressive features with a dismal outcome after conventional regimens (Martin et al. 2016).

Clinical Indications for CAR-T Cells

Following a conditional marketing authorization issued by the EMA in December 2020, Tecartus® (Gilead) is the first autologous anti-CD-19 CAR-T cell therapy that can be administered to patients with mantle cell lymphoma in Europe. Patients deemed eligible for this treatment are those with histologically verified mantle cell lymphoma resistant to or relapsing after two or more lines of treatment, including a Bruton tyrosine kinase (BTK) inhibitor.

This registration is based on the results of recently reported a multicentre phase 2 trial (Wang et al. 2020a). Briefly, 74 patients with a median age of 65 (38–79) were enrolled, and 88% were refractory to or relapsed after BTK inhibitor treatment at any time point. The CAR-T cell product could be manufactured for 71, and 68

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Table 13.1 Updated response rates (Wang et al. 2020b)

	ORR (%)	CR (%)	PFS (%)		OS (%)	
			12 m	15 m	12 m	15 m
Intent to Tx (74 patients)	85	59				
Prim analysis (60 patients)	93	67	61	59	83	76

received 2×10^6 CAR-T cells/kg on Day 0 after a conditioning regimen consisting of fludarabine (30 mg/m²/day) and cyclophosphamide (500 mg/m²/day) from Day 5 to Day 3. The overall response rate of all 74 patients (intent-to-treat population) was 85%, with a CR rate of 59%. More importantly, after 15 months, 59% of the 60 evaluable patients were still in remission (Wang et al. 2020b) (Table 13.1).

Interestingly, in contrast to conventional strategies, the percentages of patients with an objective response were consistent among key subgroups, including patients with high-risk features (Wang et al. 2020a).

Adverse events were mainly cytopenias ($\geq$ grade 3: 94%) and infections ($\geq$ grade 3: 32%). A total of 26% of the patients had grade 3 or higher cytopenias more than 90 days after the administration of KTE-X19, including neutropenia (in 16% of patients), thrombocytopenia (16%), and anaemia (12%).

These encouraging results have also been confirmed for another CAR-T cell construct (Lisocabtagene Maraleucel; Palomba et al. 2020).

Critical Evaluation

These excellent results were achieved in the context of a prospective study in highly selected patients. Recently similar results have been reported in a “real life setting” (Wang et al. 2021).

In the current algorithm of the approved indication, several other conditions must be fulfilled before implementation of this treatment: careful work-up of the patient, an experienced interdisciplinary team, and a specialized hospital with follow-up resources. In future trials, the benefit–risk ratio of this demanding treatment will be rechallenged in earlier treatment lines.

Key Points

- Patients with relapsed MCL progressing under the BTK inhibitor ibrutinib should be considered for CD19 CAR-T cell therapy.
- Effective lymphodepleting chemotherapy is needed to allow expansion of CAR-T cells.

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