Bridging Chemotherapy: Relapsed/Refractory Aggressive B-Cell Lymphoma

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To Bridge or Not to Bridge in Relapsed and Refractory (R/R) Aggressive B-Cell Lymphoma?

The time interval between leukapheresis and CAR-T cell infusion is critical for many patients with R/R B-cell lymphoma and symptomatic disease that could be fatal if left untreated during the cell manufacturing period. Often, oncologists address this dilemma with bridging therapy (BT), which may include steroids, chemotherapy, targeted therapy, or radiation therapy.

However, the R/R DLBCL patients included in the ZUMA-1 trial that led to axi-cel approval were not allowed to receive BT other than dexamethasone (Neelapu et al. 2017). In contrast, the JULIET and TRANSCEND trials leading to approval of tisa-cel and liso-cel, respectively, allowed various treatments, including systemic therapy, radiation therapy, or both (Schuster et al. 2019; Locke et al. 2019; Abramson et al. 2020). In these latest trials, bridging therapy was used in 159 (59%) of 269 patients in TRANSCEND and 92% of patients in JULIET at the investigator's discretion. Importantly, patients receiving BT are likely to have more aggressive disease and, therefore, are more likely to have other risk factors for increased rates of cytokine release syndrome, neurological events, or both, such as an increased serum lactate dehydrogenase (LDH) level, increased sum of product diameter or higher

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total metabolic tumour burden (TMTV) before lymphodepleting chemotherapy, and increased baseline C-reactive protein level.

Up to 87% of patients treated with axi-cel or tisa-cel in real-world settings required BT (Nastoupil et al. 2020; Vercellino et al. 2020). However, in most patients, bridging therapy did not result in a lower tumour burden at the time of CAR-T cell reinfusion (Locke et al. 2019).

Which Bridging Therapy?

The time between leukapheresis and infusion may vary between the USA and Europe. In France, this duration of time was described to be approximately 50 days. The median number of treatment cycles during the bridge was two cycles (range, 1–4; IQR, 1–2). Bridging therapy consisted of various immunochemotherapy or chemotherapy regimens described as high-intensity BT and low-dose BT, including chemo-free regimens. Because of lymphoma progression, 31% received more than 1 line of bridging therapy. Table 22.1 describes different BT options.

The choice will be based on

1. Evaluation of the tumour mass and growth kinetics, including the LDH level, sum of product diameter, and/or TMTV;
2. The biology of the disease, including cell of origin;
3. The type of prior lines and refractoriness or sensitivity; and
4. Patient characteristics, including comorbidities and resilience.

Table 22.1 Possible bridging therapies

No treatment: asymptomatic disease without clinically relevant tumour mass or growth
Low-intensity treatment: low disease burden (For off-label drug use, please check the local requirements)
• Rituximab-dexamethasone
• Brentuximab vedotin
• Lenalidomide
• Radiotherapy
• Single agent chemotherapy, e.g., etoposide, gemcitabine, pixantrone
High-intensity treatment: aggressive disease
• Ifosfamide-VP16 with or without rituximab
• ICE (ifosfamide-carboplatinum-etoposide) with or without brentuximab vedotin or rituximab
• GEMOX (gemcitabine-oxaliplatin) with or without rituximab
• Polatuzumab-bendamustine-rituximab
Very high-intensity treatment for rapidly progressing disease
• High-dose melphalan with autologous stem cell support
• Hyperfractionated cyclophosphamide in combination regimens, e.g., hyperCVAD

Response Rate to Bridging Therapy and Subsequent CAR-T Cell Therapy

Across the clinical trials, objective responses were achieved across all subgroups, including in patients receiving bridging therapy (Locke et al. 2019). Durable responses were also seen in patients who received BT (Locke et al. 2019). However, in real life, early relapses were associated with high-intensity BT (Vercellino et al. 2020), correlated with a higher tumour burden and more rapidly progressive symptomatic disease at the time of selection. Similarly, Nastoupil and coworkers showed that among the patients who received axi-cel infusion, bridging therapy was not associated with OS but may have negatively affected PFS, particularly among those who received systemic BT. Intriguingly, patients who received bridging radiotherapy had superior PFS vs. patients who were bridged with systemic therapy, despite comparable baseline characteristics (Nastoupil et al. 2020).

Key Points

The decisions of whether to administer bridging therapy and which bridging therapy to choose require consideration of the following factors:

- Evaluation of **the lymphoma growth kinetics** based on measurement of the tumour volume at the time of apheresis, ideally measured by total metabolic tumour volume on an 18-FDG PET scan or bulk disease (>7.5 cm) or widespread disease (Ann Arbor III or IV) evaluated on a CT scan, and elevation of LDH levels above the upper normal value (UNV).
- Integration of the **biology of the tumour** with the possibility of choosing targeted therapies, such as therapy with a monoclonal antibody (anti-CD30, anti-CD20), BTK inhibitor or lenalidomide.
- **Close monitoring of the patient**, who may not be completely under your control: a close collaboration and numerous contacts (at least 1/week) with the referring centre is mandatory.
- **All treatments** can be used based on the growth kinetics and biology of the tumour, individual patient characteristics, and prior lines, with one goal: controlling the disease up to the time of CAR-T cell reinfusion.

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