

ABOUT THE AUTHOR



Mahmoud Elsaywy, MD, MSc

Dr. Elsaywy is an Assistant Professor of Hematology and a Hematologist/Transplant Physician, Dalhousie University and Nova Scotia health, Halifax, Canada. He graduated from Cairo University School of Medicine, Egypt in 2007. He finished his Medicine and Hematology/Oncology training at NCI, Cairo University, Egypt. Following this, he was awarded a scholarship to join Fred Hutch/ UW, Seattle between 2013 and 2016 for a postdoctoral fellowship in SCT. He then joined the LBMT Program in Vancouver, BC for a clinical fellowship between 2016 and 2018 before joining the Division of Hematology and Hematologic Oncology at Dalhousie University in 2018.

He has special interests in management of myeloid malignancies in older adults and in providing Immune Effector Cell Therapy (IEC) e.g., CAR T-cell therapy. Through collaboration with an interdisciplinary team, Dr. Elsaywy and his colleagues in the Division of Hematology and Hematologic Oncology established the first CAR T-cell therapy Program in Atlantic Canada where he currently serves as the Medical Director of Nova Scotia Health IEC (CAR T-cell) Therapy

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY FOR RELAPSED AND REFRACTORY LARGE B CELL LYMPHOMA: A CANADIAN PERSPECTIVE

Introduction

Comprising approximately 40% of diagnoses, lymphoma is the most common hematological malignancy in Canada, and 80% of lymphoma cases are non-Hodgkin lymphoma (NHL).¹ Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of new NHL cases in Canada. First-line treatment with standard of care chemoimmunotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) results in a cure in approximately 60-70% of patients. Nevertheless, 30%-40% of patients will experience relapse of their disease or are refractory to first-line therapy.²⁻⁵

Among those patients with relapsed or refractory DLBCL (R/R DLBCL), about 10-15% will exhibit primary refractory disease with either stable or progressive disease despite first-line therapy, while 20-25% will experience relapse after an initial response to treatment.⁶ Most relapses will occur within 2-3 years following initial treatment. For these patients, the standard approach is salvage

chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) for those who meet the eligibility criteria and have chemosensitive disease.

Salvage Chemotherapy

There is evidence for multiple salvages, or later-line, chemotherapy regimens in the setting of R/R DLBCL. While there are no apparent outliers for optimal response, salvage regimens that include rituximab have historically been associated with slightly better outcomes.^{7,8} The CORAL study compared rituximab, dexamethasone, cisplatin, and cytarabine (R-DHAP) to rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) as salvage chemotherapy in R/R DLBCL. Patients received three cycles of either R-DHAP or R-ICE, after which those patients with chemosensitive disease received high-dose chemotherapy conditioning followed by ASCT. Overall response rates (ORR), event-free survival (EFS), and overall survival (OS) were similar for both regimens.⁹

Researchers conducted a phase III trial using a non-inferiority design that compared rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP) to R-DHAP. Again, ORR, EFS, and OS were similar between regimens, but R-GDP demonstrated lower grade 3 and 4 toxicity rates.⁷

Autologous Stem Cell Transplant

Eligible patients who achieve a partial remission (PR) or complete remission (CR) following salvage chemotherapy should proceed to ASCT if they have not been previously transplanted. Evidence for the benefit of ASCT in the R/R setting comes from the PARMA trial, which examined patients with relapsed aggressive lymphoma. Patients who had previously achieved CR with initial therapy received R-DHAP for two cycles and, in the case of chemosensitive disease, were then randomized to either receive additional cycles of R-DHAP or high-dose chemotherapy followed by ASCT. Subjects in the transplant arm had a longer 5-year EFS (46% vs. 12%) and OS (53% vs. 32%).¹⁰ Newer trials have failed to show a similarly robust response, although these trials did show a statistically significant benefit of ASCT.¹¹ The more modest response demonstrated in these newer trials is likely due to many of the patients in the PARMA trial not having received rituximab as part of their initial therapy, while in more recent years rituximab would have been standard of care for initial therapy in DLBCL. ASCT for patients with R/R DLBCL who had a PR or CR following salvage chemotherapy performs significantly better than salvage chemotherapy alone and constitutes the current standard of care in eligible patients for whom treatment is with curative intent.

In 2018, researchers published encouraging 5-year survival outcomes for patients with R/R DLBCL who had chemosensitive disease and underwent ASCT with R-BEAM conditioning, which consists of a combination of rituximab, carmustine, etoposide, cytarabine, and melphalan. The 5-year disease-free survival (DFS) and OS were 62% and 73%, respectively. In this study, neither cell of origin nor timing of disease relapse were associated with the outcome measures.¹² Patients with primary refractory disease are less likely to respond to salvage chemotherapy and are, therefore, less likely to receive an ASCT.

In contrast to patients who respond to salvage therapy and ASCT, those whose cancer is not chemosensitive to salvage therapy are not eligible for ASCT. This group of patients and those who relapse following ASCT experience exceptionally poor outcomes. The SCHOLAR-1 study retrospectively analyzed outcomes in patients with R/R DLBCL and found a median survival of 6.3 months from the start of salvage chemotherapy, with a 1-year OS of 28% and a 2-year OS of 20%.¹³ Early relapse (within 12 months) and refractory disease exhibit a worse prognosis.⁶ Of the patients who are refractory or exhibit early relapse, only 30-40% will respond to salvage chemotherapy and have the

option to proceed to ASCT, and about 50% will experience a relapse after transplantation. This confers a poor prognosis, particularly for those patients with secondary International Prognostic Index (IPI) scores >2.¹³

Chimeric Antigen Receptor T-cell (CAR-T) therapy

CAR-T therapy involves collecting patient T cells and genetically modifying these to express CARs that include an external antigen-binding domain with heavy and light single-chain variable fragments that direct specificity to an antigen expressed by cancer cells and an intracellular domain consisting of a T-cell receptor signal transduction domain and co-stimulatory domain(s) to provide activation signals to the T-cell. The CARs recognize the specific antigen independently of major histocompatibility complex (MHC) presentation, which overcomes the downregulation of antigen processing and presentation pathways, a common mechanism for immune evasion in tumours.¹⁴

Two pivotal studies, ZUMA-1¹⁵ and JULIET¹⁶, studied the outcomes in patients with R/R DLBCL who received anti-CD19 CAR-T cell therapy, and based on those results, the two tested CAR-T cell products, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, were approved in Canada for R/R DLBCL following the failure of two or more lines of therapy (**Table 1**). The ZUMA-1 trial results were published in 2017, and of the 108 patients studied, the ORR was 82%, with an OS of 52% at 18 months of follow-up.¹⁵ At 27.1 months of follow-up, the progression-free survival (PFS) was 39%, with an ORR of 83% and a CR rate of 58%. More recently updated survival analyses showed a prolonged OS of 44% after four years of follow-up.¹⁷ In a matched propensity score analysis, patients treated with the CAR-T cell therapy axi-cel in the ZUMA-1 trial had significantly longer OS compared to patients in the SCHOLAR-1 trial, with an OS of 50% and 12% at two years of follow-up, respectively.¹⁸ The JULIET trial randomized 93 patients with R/R DLBCL who were either not candidates for, or had contraindications to ASCT, or had relapsed following ASCT, with the CAR-T cell product tisagenlecleucel targeting CD19. Of those patients, 40% achieved a CR and 12% a PR. At 12 months, the RFS rate was 65% (79% among patients with a CR), and the PFS at 14 months of follow-up was 34%.¹⁶ Results of the pivotal studies are summarized in **Table 2**.

In patients who are refractory to chemotherapy, who are not eligible for ASCT, or who relapse after ASCT, consideration should be given to treatment with CAR-T therapy. Patients on salvage chemotherapy in preparation for ASCT who do not demonstrate sufficient response to the chemotherapy should also be considered for CAR-T therapy. **Figure 1** shows the treatment algorithm for relapsed refractory LBCL and where CAR-T cell therapy may be appropriate.

CAR T-Cell Therapy	Description	Indication	Health Canada Approval Date
Tisagenlecleucel (Kymriah)	CD19-directed genetically modified autologous T-cell therapy	Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after ≥ 2 lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	September 2018
Axicabtagene Autoleucel (Yescarta)	CD19-directed genetically modified autologous T-cell therapy	Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after ≥ 2 lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	February 2019

Table 1. CAR-T Cell Therapies Approved in Canada; from Canadian Evidence-Based Guideline For The Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma; Lymphoma Canada

Additionally, the role of CAR-T therapy was recently explored as an earlier line treatment for patients with R/R DLBCL and LBCL in three prospective randomized studies. In two studies, the ZUMA-7 (DLBCL) ¹⁹ and TRANSFORM (LBCL) ²⁰, anti-CD19 CAR-T cell therapy was shown to be superior to standard of care salvage chemotherapy and ASCT in the second-line treatment setting among patients who had primary refractory or early

relapsed disease (within 12 months). On the other hand, the BELINDA ²¹ study (DLBCL) did not show significant differences in outcomes between CAR-T therapy and salvage chemotherapy. **Table 3** provides an overview of the efficacy (objective response rate and event-free survival) as well as toxicities (cytokine release syndrome and immune effector cell-associated neurotoxicity) seen in these three studies.

Variable	ZUMA-1 (axi-cel [KTE-C19])	JULIET (t-cel [CTL019])	JULIET Package Insert (t-cel [CTL019])	TRANSCEND-NHL-001 (full cohort; liso-cel [JCAR017])	TRANSCEND-NHL-001 (core cohort; liso-cel [JCAR017])
No. pheresed	111	165	160	134	NR
No. treated	101	111	106	114	NR
No. evaluable	101	93	68	102	73
No. never treated (%)	10 (9) of 111	50 (31) of 161	49 (30) of 160	20 (15) of 134	NR
Bridging treatment, %	0	92	90	NR	NR
ORR, %	82	52	50	75	80
CR, %	54	40	32	55	59
6-Month ORR, %	41	37*	NR	NR	47
6-Month CR, %	36	30*	NR	NR	41
ITT ORR (%)	83 (75) of 111	48 (30) of 161	N/A	77 (63) of 122	NA

Table 2. Efficacy of Anti-CD19 CAR T Cells in Aggressive B-NHL; adapted from Caron, A. et al, 2019

Abbreviations: axi-cel, axicabtagene ciloleucel; B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; CR, complete response; ITT, intent-to-treat; liso-cel, lisocabtagene ciloleucel; NA, not applicable; NR, not reported; ORR, objective response rate; t-cel, tisagenlecleucel.

*Numbers reflect an earlier presentation of the JULIET trial.⁸

	ZUMA-7¹⁹	TRANSFORM²⁰	BELINDA²¹
Number of patients	359	184	322
Primary refractory (N)	74	73	66
crossover	No	Yes	Yes
ORR (CAR T)	83	86	46
EFS (in months)	8.3	10.1	3
CRS (N)	92	49	59
ICANS (N)	60	12	10

Table 3 Overview of efficacy and toxicities in three pivotal anti-CD19 CAR-T cell therapy trials; courtesy of Mahmoud Elsayy, MD, MSc

CAR: chimeric antigen receptor; CRS: cytokine release syndrome; EFS: event-free survival; ICANS: immune effector cell-associated neurotoxicity; ORR: objective response rate

Real-world results

Several real-world and registry data have replicated the results reported in the above-described pivotal trials. Among 298 patients who underwent leukapheresis for CAR-T manufacturing in several US centers, 275 (92%) actually received an anti-CD19 CAR-T cell therapy product. The best ORR and CR rates observed in infused patients were 82% and 64%, respectively. At a median follow-up of 12.9 months from the time of CAR T-cell infusion, the median PFS was 8.3 months, and the median OS was not reached.²²

Practical considerations for anti-CD19 CAR-T cell therapy

Eligibility criteria

Recently, a group of Canadian lymphoma and cell therapy specialists published a consensus recommendation on the eligibility criteria for anti-CD19 CAR-T cell therapy. The consensus recommendations included that patients eligible for intensive therapy following failed salvage therapy or failed stem cell transplant, should receive anti-CD19-targeted CAR-T cell therapy according to the criteria listed below.²³

Indications for ICU admission for patients with CRS and/or ICANS²⁶	High-risk patients for severe CRS and ICANS	General management guidelines in ICU
SBP < 90 mmHg requiring vasopressors; OR • Hypoxia/respiratory distress with increasing oxygen requirement ($\geq 6\text{L O}_2/\text{min}$) or need for ventilatory support; OR • Clinically significant arrhythmias or acute coronary syndrome with positive troponin; OR • ICE-score ≤ 6 points, signs of raised ICP or seizures; OR • Team concern particularly for high-risk patients	• Older age (≥ 65 yrs) • Early onset CRS (<24 hr) • Coexisting comorbid conditions (e.g. renal, CVS) • High tumor burden • High pretreatment LDH • High pretreatment inflammatory markers (ferritin, CRP)	• The use of tocilizumab (anti-IL6R) and/or steroids should be done in close consultation with the transplant team • Supportive management of organ toxicities as per standard guidelines • Assess for infection (blood/urine cultures, chest x-ray, ICANS: lumbar puncture, and start empiric antibiotic therapy if not already started • Laboratory: creatinin, urea, LFTs, WBC, LDH, ferritin, and CRP daily until 72 hrs after symptom improvement • Consider formal echocardiography (recommended for prolonged severe CRS >72h) • ICANS: CT/MRI, EEG, neuroprotective care, consider ICP monitoring • Neurology team should be closely following patients with ICANS

Table 4. Intensive care indication, risks, and general management for patients experiencing CRS or ICANS; courtesy of Mahmoud Elsayy, MD, MSc

CRP: c-reactive protein; CRS: cytokine release syndrome; CT: computed tomography; EEG: electroencephalogram; ICANS: immune effector cell-associated neurotoxicity; ICE: immune effector cell encephalopathy; ICP: intracranial pressure; LDH: lactate dehydrogenase; LFT: liver function test; MRI: magnetic resonance imaging; SBP: systolic blood pressure; WBC: white blood cell count

ELIGIBILITY CRITERIA

- Patient has received ≥ 2 lines of systemic therapy
- Good performance status (ECOG ≤ 2)
- Not received prior adoptive T cell immunotherapy
- No active central nervous system (CNS) disease
- No significant compromise to vital organ function (as defined per institutional guidelines)

Additionally, as per Health Canada approved indications for CAR-T therapies, patients must meet the following criteria²³:

HEALTH CANADA APPROVED INDICATIONS FOR CAR-T CELL THERAPIES

- R/R DLBCL of the following subtypes, after ≥ 2 lines of systemic therapy:
- DLBCL, not otherwise specified
- High-grade B-cell lymphoma
- High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement
- DLBCL arising from follicular lymphoma
- Primary mediastinal large B-cell lymphoma (PMBCL)

* Relapsed disease is defined as partial or complete response to the last line of therapy and subsequent progression

* Refractory disease is defined as progressive or persistent disease as the best response to the previous therapy

Bridging therapy

Patients undergo leukapheresis before CAR-T therapy and manufacturing of CAR-T cells usually takes several weeks. During this time, if there is a concern for, or evidence of, progressive disease that is causing symptoms or worsening of clinical status, patients would likely benefit from bridging therapy while awaiting CAR-T treatment. Agents to consider for bridging to CAR-T therapy include⁶ single-agent treatment with cyclophosphamide, cytarabine, gemcitabine, or other salvage regimens. Localized radiation therapy may also be beneficial for bulky or symptomatic disease. Furthermore, single-agent steroids could also be utilized. Currently polatuzumab vedotin with bendamustine and rituximab is approved as an effective bridging regimen prior to CAR-T cell therapy.²⁴

Considerations for toxicity management

CAR-T cell therapy is associated with two unique acute toxicities, which can be severe and even life-threatening. Cytokine release syndrome (CRS), the most frequently occurring toxicity, can present with low-grade constitutional symptoms or a high-grade syndrome associated with life-threatening multiorgan dysfunction; rarely, severe CRS can evolve into fulminant hemophagocytic lymphohistiocytosis. Immune effector cell-associated encephalopathy syndrome (ICANS) is the second most common adverse event and can occur concurrently with or after CRS. These adverse events require intensive monitoring, accurate grading, and prompt management with aggressive supportive care, anti-IL-6 receptor therapy, and/or corticosteroids.²⁵

Prompt recognition and urgent aggressive intervention for the management of CRS or ICANS are key elements for successful outcomes and lead to shorter ICU stays. Almost all CRS/ICANS are reversible with adequate and timely supportive measures. Deteriorations in patient status are

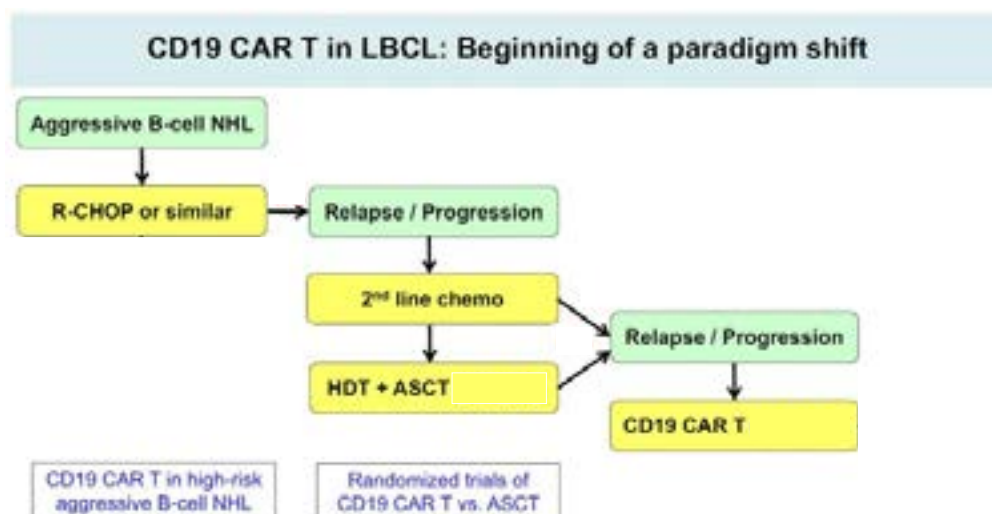


Figure 1, Treatment algorithm in LBCL; Adapted from S. Neelapu, WHU 2021 Presentation.
<https://careeducation.ca/dr-sattva-neelapu-cell-therapy-whu-2021/>

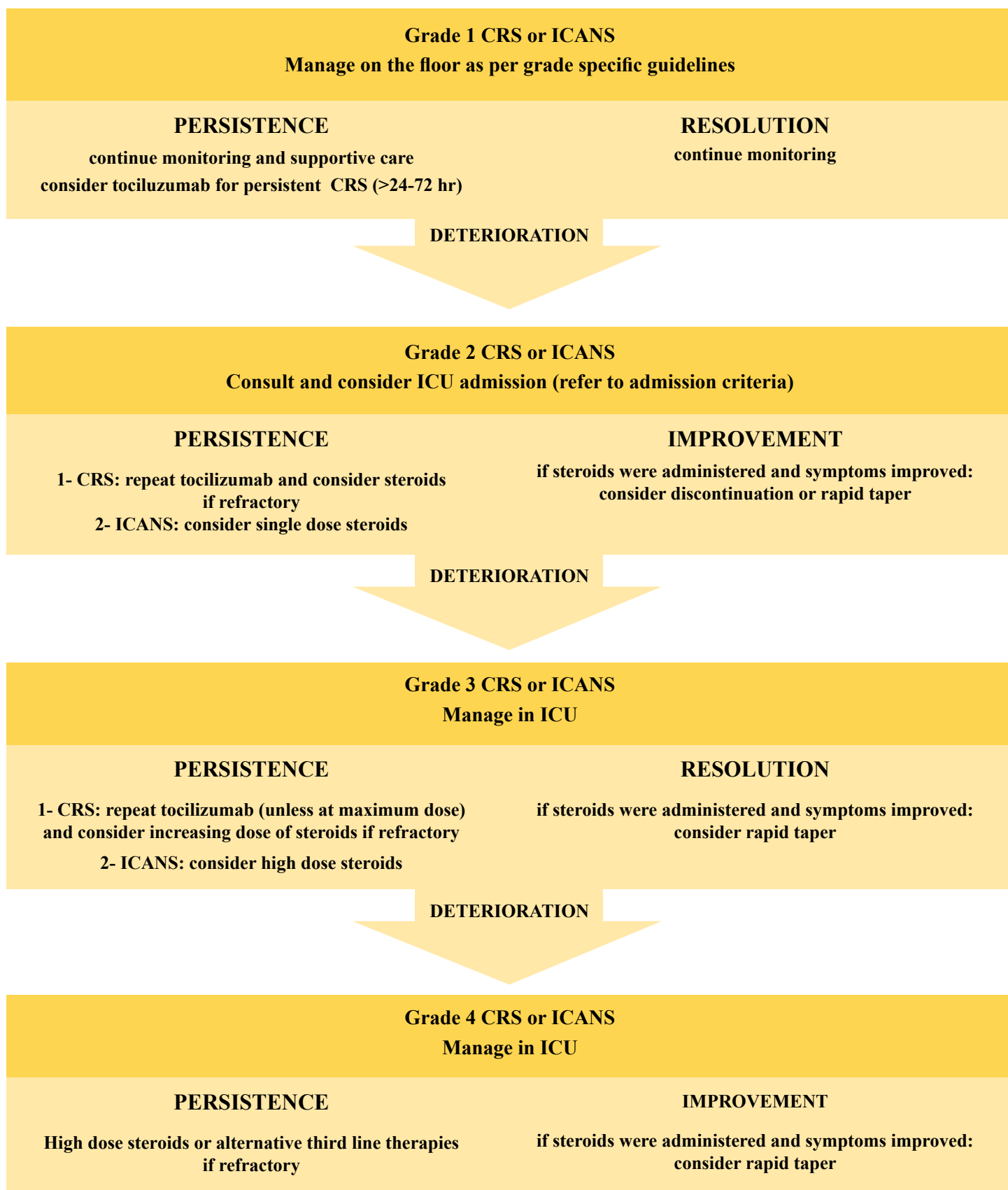


Figure 2 Indications for ICU admission and general ICANS management guidelines; courtesy of Mahmoud Elsayy, MD, MSc

quick and dramatic. Higher grade CRS is characterized by rapidly progressive capillary leak syndrome. Managing persistent hypotension with overt fluid management leads to inferior results versus early initiation of vasopressors.^{26,27} Supportive care is the mainstay of ICANS management. Indications for ICU admission and general management guidelines are outlined in **Table 4** and **Figure 2**. Details of grading and specific management guidelines are discussed elsewhere.²⁵

Summary

DLBCL is considered a curable disease with frontline therapy. Nevertheless, a significant proportion of patients will still experience disease relapses or are refractory to frontline treatment. The standard recommended therapy for this patient population is salvage therapy followed by ASCT. However, this treatment approach may still fail in achieving cures for a significant proportion of patients with R/R DLBCL. In addition, a subset of patients is ineligible for ASCT, not responsive to salvage chemotherapy, or will relapse post-ASCT. This patient group has a poor prognosis and requires effective treatment strategies. CAR-T cell therapy has revolutionized the treatment for those patients and provides a potential cure with long-term follow-up results supporting durable response with no new safety concerns. The arrival of this novel therapy has undoubtedly led to a positive change in the natural history of this disease with an otherwise grave prognosis. Furthermore, real-world data have confirmed pivotal trial results, adding another layer of evidence supporting the use of this treatment modality. The earlier application of CAR-T cell therapy during the treatment of patients with R/R DLBCL was investigated in trials and may potentially change the standard of care for those patients who relapse early or who are refractory to first-line therapy.

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