DIFFUSE LARGE B-CELL LYMPHOMA
LANDSCAPE ANALYSIS
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**Brief Overview**

The most common sub-type of non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL) accounts for 30% of cases of NHL in the US.\(^1\) DLBCL is an aggressive disease affecting B-lymphocytes. Lymphocytes make antibodies that help to fight infections. When abnormal lymphocytes divide but do not fully develop, they are unable to fight infections.

Lymphoma causes a build-up of abnormal B-cells (lymphocytes) most commonly in lymph nodes or bone marrow.\(^2\) B-cell lymphoma can also occur outside of the lymph nodes, known as "extranodal sites." Extranodal sites include the spleen, bone, brain, skin, thyroid, gastrointestinal tract, and other soft tissues.

DLBCL is considered a potentially curable disease, despite being aggressive. The US sees 30,000 new cases annually.\(^3,4\) Incidence increases with age.

**Unmet Needs**

**Newly Diagnosed**

DLBCL occurs in people of all ages, however it is most prevalent in older adults (aged 55 and over).\(^5\) Median age at diagnosis is age 66, and people are most often diagnosed between ages 65 and 74 (Figure 1).\(^7\) Approximately 96% of NHL are caused by random replication errors in deoxyribonucleic acid (DNA).\(^6\) These mutations can occur at any age, but occurrence increases with age. Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program highlights the increase of DLBCL prevalence as people age.

The aging population has similar characteristics such as comorbidities, life expectancy, physical fitness, and socio-economic status.\(^8\) With comorbidities comes polypharmacy (ie, the use of multiple medicines), which increases the risk for drug interactions with lymphoma treatments. Additionally, people aged 80 and above more commonly face issues such as falls, cognitive decline/dementia, and loss of autonomy, which has been correlated with shorter life expectancy.

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**FIGURE 1. SEER Data on New Cases of DLBCL by Age (SEER)**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Percent of New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.2%</td>
</tr>
<tr>
<td>20-34</td>
<td>5.3%</td>
</tr>
<tr>
<td>35-44</td>
<td>6.2%</td>
</tr>
<tr>
<td>45-54</td>
<td>11.1%</td>
</tr>
<tr>
<td>55-64</td>
<td>21%</td>
</tr>
<tr>
<td>65-74</td>
<td>26.6%</td>
</tr>
<tr>
<td>75-84</td>
<td>20.2%</td>
</tr>
<tr>
<td>&gt;84</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

**Median Age at Diagnosis**

66 years old
There are three predictive factors for mortality among older adults treated for cancer, including:

- Physical capacity – such as performance status or evaluation through the Timed Up and Go (TUG) screening.
- Nutritional deficiencies – refers to when the body is not getting enough nutrients such as vitamins and minerals.
- Comorbidities - refers to the presence of multiple medical conditions in addition to the cancer.

Providers are efficient at evaluating each of these three predictive factors. Areas of unmet need in patients with DLBCL, however, include evaluating psychological cognitive function and socioeconomic status.

Cognitive function refers to the process of learning, understanding, and communicating. Various factors impact cognitive functioning for patients such as health literacy level, side effects of medications or treatment, previous brain injuries, age, and comorbidities. A study published in Haematologica found that in a population of lymphoma patients considered clinically fit, 30% had cognitive issues when assessed with the Mini Mental State Evaluation (MMSE), and 51% had abnormal results on the Montreal Cognitive Assessment (MoCA). As a result, study authors recommended cancer care providers collaborate with geriatricians and primary care providers to better understand patient needs and help improve their quality of life.

Patient socioeconomic status (SES) is another area of unmet need. Socioeconomic status can significantly impact how a patient handles unexpected adverse events, hospital visits, and/or the high cost of medications. Studies examining SES and DLBCL often do so in relation to treatment. Earlier studies found patients with DLBCL who lived in neighborhoods with low SES had significantly lower rates of survival. This was especially true for patients who were younger (not Medicare eligible) and married. Study authors identified inadequate insurance coverage and additional financial burdens as barriers to effective treatment among patients with low SES.

A more recent study examined SES factors in relation to treatment with CAR T-cell therapy for patients with relapsed/refractory (R/R) DLBCL. Study results showed unemployment was a significant predictive factor for poor overall survival in patients treated with CAR T-cell therapy.

**Relapsed/Refractory Disease**

Approximately 10% to 15% of patients with DLBCL will have refractory disease, and 30% to 40% will relapse within the first two years after treatment. The largest unmet need for these patients is the poor prognosis associated with R/R DLBCL. Historically, approximately 50% of transplant-eligible patients could be cured through high-dose chemotherapy and autologous stem cell transplant (HDCT-ASCT). More recent evidence shows that transplant-eligible patients with early relapse or primary-refractory disease derive greater benefit from CAR T-cell therapy (ie, axi-cel or liso-cell) than traditional platinum-based salvage chemotherapy followed by consolidative HDCT-ASCT.

For patients who decline transplant or are ineligible for HDCT-ASCT (due to age, comorbidity, or failure of salvage chemotherapy), treatment options are limited in efficacy. Patients fit enough to receive CAR T-cell therapy may see benefit: the product Liso-cel is approved for use in the second-line for patients who are not transplant-eligible, and 3 products (Axi-cel, Tisa-cel, and Liso-cell) are approved for use in the third-line, regardless of transplant eligibility or receipt. Other options including novel therapies may also be considered.

In addition, there is a significant unmet need regarding costs incurred by patients associated with treatment after the first year following diagnosis. Within the first 12 months following treatment initiation, patients who are failed by first-line treatment and are transplant-ineligible have very high health care utilization and costs. A study examining the economic burden of DLBCL patients who are on Medicare showed a significant portion of Medicare beneficiaries (individuals 65 and above) require therapy beyond the first-line setting, at a high cost to the patient.

A retrospective study examined 5,909 Medicare beneficiaries who completed first-line treatment for DLBCL. There were 1,552 claims indicating second-line therapy during follow-up among the relapsed group. Average follow-up time after first-line treatment was similar regardless of relapse (915 days) or no relapse (929 days).
However, compared to non-relapsed patients, patients who relapsed had:

- **Increased claims for hospital admissions**: 61% vs. 41%
- **Increased emergency room visits**: 52% vs. 43%
- **Higher utilization of skilled nursing facilities**: 19% vs. 13%
- **Higher use of home health agencies**: 36% vs. 23%
- **Higher use of hospice services**: 20% vs. 6%

Cost factor comparisons showed that compared to non-relapsed patients, patients who relapsed had:

- **Higher inpatient costs**: $1,147 vs. $511
- **Higher outpatient office visit costs**: $3,036 vs. $691
- **Higher ambulatory costs**: $1,730 vs. $343

Overall, there were higher total health care costs attributable to the relapsed group when compared to non-relapsed ($6,566 vs. $1,951). These data suggest higher health care utilization and costs in patients with relapsed DLBCL in a Medicare population. Cost estimates for treatment of R/R disease are expected to rise as the number of patients receiving more expensive treatments (eg, CAR T-cell therapy, etc.) continues to increase.

**Supportive Care**

As stated above, many hematological cancers require intensive and long-term treatment, with associated needs for supportive care. A retrospective analysis reviewed 20 studies on the toll of hematological diseases on patients between 2009 and 2020. Patient supportive care needs included informational, physical, psychological, daily living, and sexual; though sexual and spiritual unmet needs were reported at low levels.
Many patients with lymphoma face psychological distress and poor quality of life throughout their illness. Informational need was defined as concern regarding information about their future conditions. Psychological and emotional needs correlated with distress, worry, anxiety, and depression. Physically, patients’ concerns focused on sexual issues, fatigue, pain, insomnia, and neuropathy in hands and feet. Daily living concerns included handling medical and living expenses, employment, and health insurance status.

The article found specific predictive factors for unmet supportive care needs, which included type of hematological malignancy, age at diagnosis, marital status, gender, income, and pre-existing anxiety and/or depression. Screening for and understanding patient supportive care needs is crucial to improving satisfaction as well as quality of life. Screening tools include but are not limited to distress, food insecurity, and depression screeners.

Recent Advancements

**Newly Diagnosed**

Since 2006, the standard of care for front-line treatment of DLBCL in fit patients has been rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). In patients with high-risk large B-cell lymphoma subtypes, such as high-grade B-cell lymphoma (HGBCL) with translocations of MYC and BCL2 (commonly referred to as “double-hit” lymphoma), intensified chemo-immunotherapy regimens such as dose-adjusted R-EPOCH are used. However, in April 2023, the U.S. Food and Drug Administration (FDA) approved polatuzumab vedotin-piiq, an antibody-drug conjugate, to be used in combination with R-CHOP.

**FIGURE 2. Novel agents for the treatment of patients with R/R DLBCL**

![Image of novel agents for treatment of R/R DLBCL]
with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (pola + R-CHP) for patients who have untreated DLBCL or HGBCL, not otherwise specified, and an International Prognostic Index (IPI) score of 2 or greater. In the randomized trial leading to approval of pola + R-CHP in this setting, patients who received pola + R-CHP had a higher 2-year progression-free survival than patients who received R-CHOP (76.7% vs. 70%), but no differences in overall survival have yet been observed.

Studies are ongoing to investigate whether bispecific antibodies and antibody drug conjugates are beneficial in frontline therapy.5

**Relapsed/Refractory Disease**

Treatment of relapsed DLBCL in the second- and third-line is largely dependent on whether the patient is eligible for autologous transplant and/or CAR-T therapy. Fifty percent (50%) of patients with R/R DLBCL are ineligible for salvage therapy and stem cell transplant.20 Transplant ineligible patients are further segmented into categories of appropriate or inappropriate to receive CAR T-cell therapy. Importantly, patients with progression or relapse of DLBCL within 12 months of first-line treatment are recommended to undergo CAR T-cell therapy regardless of transplant eligibility.21

Historically, consolidative high-dose chemotherapy followed by ASCT was standard of care for patients with relapsed DLBCL who demonstrated sensitivity to second-line salvage chemotherapy (eg, with RICE). The ZUMA-1 and TRANSFORM studies enrolled transplant-eligible DLBCL patients with progression or relapse within 12 months of frontline therapy and randomized them either to standard of care with salvage chemotherapy followed by consolidative HDCT-ASCT, or to CAR T-cell therapy. Both studies showed that CAR T-cell therapy improved progression-free survival (PFS) compared to ASCT, and ZUMA-1 has now shown a definitive overall survival advantage for CAR T-cell therapy with axi-cel. Notably, only 1/3 to 1/2 of patients intended for HDCT-ASCT received the transplant on these studies, often due to failure to respond to salvage chemoimmunotherapy. For DLBCL patients who relapse >12 months after frontline therapy, salvage chemoimmunotherapy followed by consolidative HDCT-ASCT remains the standard of care in transplant-eligible patients. For those who do not have primary refractory DLBCL, ASCT remains standard of care if the DLBCL is sensitive to chemotherapy. Only half to one third of patients who intend to go for ASCT could receive an ASCT.

For patients with relapsed DLBCL who are ineligible for transplant in the second line, several options may be considered. Transplant ineligible patients with relapsed DLBCL who are eligible for CAR T-cell therapy should be considered for liso-cel, which is approved in this setting. Alternatively, the tafasitamab-lenalidomide regimen is approved for patients with R/R DLBCL who are ineligible for transplant.22 Approval was based on the L-MIND study, which showed a median PFS of 12 months in patients with R/R DLBCL treated with 1-3 prior lines of therapy. The FDA approved polatuzumab vedotin plus bendamustine and rituximab (pola + BR) to treat R/R DLBCL who have failed two or more lines of therapy based on results of the GO29365 study.20 Recently, the FDA approved two CD20-CD3 bispecific antibodies, epcoritamab and glofitamab, as treatment for R/R DLBCL who have failed two or more lines of therapy.23 In addition to newly approved treatments, clinical trials are showing preliminary success with cancer vaccines if used in combination with immunotherapy drugs. More trials are necessary before this treatment is approved for use in broader patient populations.

Clinical trials should always be considered when treating relapsed DLBCL. One other important advancement in cancer treatment is precision medicine. In addition to investigating new therapies, ongoing studies aimed at utilizing genomic profiling and novel methods for detecting disease relapse to improve outcomes for patients.
Symptomatic Clinical Presentation

Common symptoms for DLBCL include:\(^2^4\)
- Quick growing, non-painful mass, or lymph node(s)
- Fever
- Weight loss
- Night sweats

Other symptoms may include anorexia, pedal edema, fatigue, and shortness of breath.\(^2^4\)

Treatment Toxicities

Patients who are treated with a standard R-CHOP or pola + R-CHP regimens in 1L DLBCL have the potential for the following short-term toxicities:\(^2^5\)
- Hematologic toxicities
- Febrile neutropenia
- Cardiac toxicity
- Peripheral neuropathy

Long-term toxicity with R-CHOP includes low rates of secondary myelodysplasia or acute myeloblastic leukemia (MDS or AML), functional and cognitive decline, late heart failure, and diabetes.\(^2^5\) Long-term toxicity data are not yet available for pola + R-CHP.

In addition, newer immuno- and cellular therapies such as bispecifics and CAR T-cell therapy require increased monitoring, upskilling, and operationalization at therapy initiation and during short-term follow-up, to prevent and/or treat their specific toxicities, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Despite this realization, clinical trials of different CAR T-cell therapy products have not been designed on CRS grading scales and management algorithms. Thus, there is the urgent need to design clinical trials of different CAR T-cell therapy products to pave the way for more efficacious and safe utilization of CAR T-cell therapy for patients with R/R DLBCL.\(^2^6\)
Non-Clinical Challenges in Treating DLBCL Patients

Non-clinical factors that impact cancer mortality for patients with DLBCL include low socioeconomic indicators such as lack of health insurance and access to care. Individuals with low socioeconomic status (SES) are less likely to have insurance coverage, are underinsured, and are less likely to pay high out-of-pocket costs for treatments. Individuals with low SES may also be less likely to access high-quality treatment and follow-up care, resulting in increased mortality rates.

In addition, financial burden is high for patients with DLBCL, regardless of SES. Treatment costs may include chemotherapy, immunotherapies, radiation treatment, and outpatient prescription costs. A recent study found the largest contributors to health care utilization among this population were outpatient/office visits, radiation therapy, and inpatient admissions within the first year of diagnosis.

The same study ran a simulation model to identify costs attributable to patients who are treated for DLBCL. Mean total cost (calculated as total cost divided by the total number of patients) per patient was $31,499.28 When assessing cost by subgroups, the authors found the total average cost ranged from $5,017 for patients on palliative care alone to $135,493 for patients receiving an autologous HCT as second line treatment.

Multidisciplinary Care

Utilizing a multidisciplinary team (MDT) has been shown to support better patient care, especially in cancer settings. Achieving multidisciplinary care involves collaboration between multiple professionals.

A multidisciplinary care team for the treatment of DLBCL usually encompasses:

- Hematologist/Oncologist
- Radiologist
- Clinical nurse specialist (CNS)
- Pathologist
- Others – may include radiation oncologist, clinical pharmacist, advance practice provider(s), research coordinator(s), dietitian, social worker, physiotherapist, occupational therapist, or psychologist

This collaboration can be grouped into 4 categories:

- Communicating with other professionals
- Exchanging information
- Managing team members
- Encouraging active participation
Due to the aggressiveness associated with DLBCL, prompt diagnosis and treatment are vital to favorable patient outcomes and depend on the collaboration of various providers. Additionally, because this disease often requires multiple lines of treatment, care coordination between inpatient and outpatient teams is critical.

Conclusion

Diffuse large B-cell lymphoma (DLBCL) is an aggressive disease whose management is complex and requires open communication amongst a multidisciplinary care team. It has a high rate of relapse, with up to 40 percent of patients relapsing within the first two years after primary treatment. Management of a patient with DLBCL begins with prognostic evaluation of the disease and assessing the potential adverse effects of treatments. It should be followed by evaluations of physical, physiological, cognitive, and socio-economic status of the patient. When considering treatment options, the patient should be engaged to share their expectations and goals related to disease control and quality of life.

There are many clinical trials that are testing novel treatments for DLBCL. Undoubtedly, the future of treatment for newly diagnosed DLBCL and R/R DLBCL will look different over the next few years. Health care providers should be cognizant of a patient’s physical, psychological, and SES when choosing which treatment options to use. Clinical trial data, along with real-world data, will help to inform treatment decisions, improve clinical outcomes, and preserve quality of life for patients.

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