Review Article

Disparities in lymphoma on the basis of race, gender, HIV status, and sexual orientation

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Abstract: Lymphoid malignancies account for the sixth leading cause of death in the US, and, although survival is improving overall, this trend is not applicable to all patients. In this review, we describe disparities in the initial presentation, treatment, and outcomes across a diverse group of lymphoma patients on the basis of gender, race, HIV status, and sexual orientation. Identifying these disparities will hopefully lead to improved outcomes in these groups of lymphoma patients in the future.

Keywords: Lymphoma disparities; sexual minority group; HIV lymphoma; fertility preservation; pregnancy

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Introduction

Collectively, lymphoid malignancies account for more than 130,000 new diagnoses per year and represent the sixth leading cause of cancer death in US (1). Although, as a group, the incidence is decreasing and the survival is increasing, these trends are not applicable to all populations. Despite the tremendous advances in the management of lymphoid malignancies in recent years, disparities in numerous areas remain (1). Disparities on the basis of gender, age, socioeconomic status, race, sexual orientation, and many other areas have been found to affect all aspects of the management of various lymphoid malignancies from diagnosis, treatment, and survivorship. Recognition of disparities in these areas is critical to increase recruitment of these populations to clinical trials and observational studies in an effort to improve survival.

Methods

We conducted a comprehensive literature search using PubMed, Cochrane Library, and MEDLINE databases. Searches took place at the time of the original submission of this review in May of 2017 as well as at the time of final submission in October 2017. We included articles written in English that included the search terms of interest within the title and/or abstract. Articles without full text access were excluded. For each category, various combinations of the following terms were searched: "lymphoma", "cancer", "malignancy", "outcomes", "survivorship", "disparities". The following search terms added to the above terms were tailored to each sub-category:

Racial disparities: "race", "ethnic minority", "anthracycline cardiotoxicity".

Gender disparities: "female", "pregnancy", "fertility preservation", "gender", "radiation".

HIV and sexual/gender minorities: "HIV", "sexual and gender minorities", "lesbian", "gay", "bisexual", "transgender", "queer", "men who have sex with men", "sexual orientation", "homosexual", "same-sex", "marital status".

The above search yielded 45 peer-reviewed manuscripts relevant to the scope of this review and subsequently included in the following review.

Racial disparities

In general, the incidence of lymphoid malignancies is lower in racial minority groups; however, differences in presentation and survival remain. For example, studies suggest that black patients generally present at younger ages and with more advanced disease at the time of presentation (2,3). This observation holds true for various types of lymphomas. In an observational study of patients with follicular lymphoma, Nabhan *et al.* reported that black patients often presented at less than 45 years of age; however, the median age of presentation in whites at the time of data collection was 64 years of age (4). Black patients are also more likely to present with features of high risk disease and high risk Follicular Lymphoma International Prognostic Index (FLIPI) scores. Hispanic patients have an increased incidence of grade 3 disease, which is important given the controversy in management of grade 3 follicular lymphoma. Similar observations have been noted in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Black patients with CLL/SLL often present with worse prognostic indicators such as increased beta-2 microglobulin levels, worsening anemia, higher Rai stage, and unfavorable cytogenetic markers compared to white patients (5,6). Additionally, Coombs *et al.* noted that black patients with CLL/SLL have a decreased event free survival and overall survival (OS) compared to white patients (5). Within cutaneous T cell lymphomas, black patients have an increased incidence of mycosis fungoides. These patients often present with a more aggressive course, higher stage, and present 10 years younger than white patients (7). Furthermore, traditionally used prognostic models, such the International Prognostic Index (IPI) in diffuse large B cell lymphoma (DLBCL) patients and FLIPI in follicular lymphoma, are not reliably applicable to black patients as compared to white patients, possibly secondary to different tumor biology, although the specifics of these differences have yet to be fully elucidated (8).

Race has been found to be an important factor in both management decisions, as well as in survivorship. In a recent study, black patients treated for Hodgkin lymphoma (HL) were found to have a greater than 2-fold increased risk of cardiovascular mortality compared to whites (9). African American race has been noted to be an independent risk factor for anthracycline-associated cardiotoxicity (10). Some data suggest that black patients receiving anthracyclines, particularly those with additional cardiovascular risk factors such as diabetes and hypertension, as well as the use of concomitant radiation, may benefit from the use of liposomal anthracycline formulations, as well as the use of prophylactic beta blockers and angiotensin converting enzyme inhibitors (9,11). As anthracyclines are a mainstay in many chemotherapy regimens for both Hodgkin and non-Hodgkin lymphomas (NHL), further research is needed in this area, particularly among minority populations, given that current guidelines for anthracycline-associated cardiotoxicity prevention are based solely on expert opinion using data from largely white and male populations (10,11).

Gender disparities

The incidence of lymphomas as a whole, with the exception of marginal zone and follicular lymphoma, is higher among men, which may stem from the fact that environmental factors and workplace exposures that are often linked to lymphomagenesis tend to occur in historically male-driven industries (1). Recent evaluation by Nabhan *et al.* suggests that in patients with follicular lymphoma, women less than 50 years of age had an improved OS compared to males, while women older than 80 years of age had better OS and progression free survival (PFS) compared to males of the same age (12). These findings may be a reflection of the fact that women in the general population of the US have an improved survival compared with men. With respect to treatment differences, Nabhan and colleagues also noted that women with follicular lymphoma were more likely to receive single agent rituximab and were less likely to receive anthracycline-based chemotherapy such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Despite possible under-treatment, women were still found to have an improved survival. The disparities within anthracycline use however are less pertinent in recent years given the increasing use of non-anthracycline-based regimens such as bendamustine-rituximab, rituximab-lenalidomide, and an increased focus on immunotherapy and targeted therapies (12). Long-term follow-up studies note that men treated for HL were found to have a higher risk of cardiovascular mortality and myocardial infarction compared to women who received similar treatment (9,13).

Female patients with lymphoma may be faced with unique treatment challenges with respect to pregnancy and fertility that may lead to disparate care compared to male patients. As a group, lymphoma accounts for 11% of malignancies diagnosed during pregnancy, but given the many presentations at diagnosis and differences in the natural history of each of these entities, little data exists to

guide the management of these women. This poses unique challenges to the care of both the mother and the unborn fetus (14,15). Although the goal of treatment is to provide the mother with optimal care while balancing the risks to the fetus, the patient and her providers often encounter many challenges at all stages of management from diagnosis to treatment (14).

Traditional imaging modalities for staging, such as computed tomography (CT) and positron emission tomography fused with CT images (PET/CT), should be avoided given the risk of exposure of the fetus to radiation. Imaging is generally limited to non-contrast enhanced MRI as both iodine-based and gadolinium contrast materials are teratogenic (14,16). Further challenges exist given conflicting data surrounding the safety during pregnancy of rituximab, which is the backbone of treatment for many types of lymphoma. Some studies report that rituximab can safely be administered during pregnancy, while others note concerns for increased hematologic and pulmonary fetal risk. Furthermore, providers are often hesitant to administer rituximab to pregnant patients out of concern for possible fetal harm in the event of an infusion reaction (17). Aside from the treatment itself, timing of treatment is often a challenge faced when treating pregnant women with cancer as, ideally, chemotherapy should be delayed if possible until the second trimester to allow for fetal organogenesis (8,15). In the largest retrospective study of pregnant lymphoma patients treated with non-anti-metabolite chemotherapy, Evens *et al.* noted an overall response rate of 82% and a complete response rate of 64%, which suggested that pregnant women could be successfully treated with chemotherapy and achieve similar outcomes to non-pregnant patients. Additionally, there was no significant difference in either prenatal or postnatal complications between women treated during the second trimester of pregnancy versus those who deferred treatment until delivery, and a low miscarriage rate of 1.1% was noted (18). A more recent study by Pinnix *et al.* notes an overall miscarriage rate of 10%, but it should be noted that these miscarriages occurred in patients requiring treatment during the first trimester of pregnancy (14,15).

Many studies have shown that in the setting of a well-experienced multidisciplinary team of oncologists, maternal fetal medicine providers, radiation oncologists, and medical ethicists, pregnant patients with lymphoma experience no difference in OS based on the timing of therapy administration, no increased risk of pregnancy complications, and no increased risk of fetal abnormalities (14,15). Additionally, studies have demonstrated that the risk of fetal neurocognitive deficits are related to shorted gestational duration (preterm delivery) rather than chemotherapy exposure itself. The difference in miscarriage rates and the challenges encountered while trying to balance the treatment of both the mother and the unborn fetus underscore the reasons why the management of pregnant patients with lymphoma should be a multidisciplinary effort by providers with experience in treating these patients (16). The use of radiation should ideally be avoided during pregnancy given the possible risks to the fetus, but in the setting of urgent situations such as superior vena cava syndrome and cord compression, radiation should be considered. However, with appropriate preventative measures such as fetal shielding, radiotherapy has not demonstrated any major adverse effects to the fetus when administered during pregnancy (14,15). These data suggest that in experienced hands, both chemotherapy and radiation can be safely administered during pregnancy. This raises the question of the outcomes for both the pregnant woman and the unborn fetus when treatment occurs at less experienced centers however. In cases where women are unable to seek the expertise of an experienced multidisciplinary team, perhaps as a result of the patient's socioeconomic status or a decreased access to appropriate services in rural areas, there remains a concern for under-treatment of these women, leading to worse outcomes.

As the treatments of malignancies in general are improving and outcomes are increasing, issues of survivorship, such as fertility preservation, are coming to the forefront in the overall management of cancer survivors. This area is particularly important within the treatment of patients with HL given the bimodal distribution of presentation. Reproductive concerns and infertility have been associated with decreased quality of life in cancer survivors (19). Studies suggest that cancer survivors are less likely to have biological children compared to age-matched controls. Importantly, female survivors are 10% less likely to have biological children compared to male survivors (19). National guidelines released in 2006 by the American Society of Clinical Oncology (ASCO) state that all patients of reproductive age should be offered fertility preservation options prior to treatment; however, several studies indicate that women are offered fertility counseling less frequently than men. As few as 4% of female cancer survivors studied in the US have undergone fertility counseling (20). Additionally, studies evaluating women who received counseling prior to treatment noted that many

women felt that the counseling was hasty, not informative, and often occurred only after the patient herself, not the provider, broached the topic (21). Fertility preservation is a more complex and timely process for women compared to men, and the success rate of generating a future pregnancy is much less certain for methods of fertility preservation available to women compared to the reliability of sperm banking for men (19,21). The process of collection for women can take several weeks, which may potentially delay the initiation of chemotherapy and is, therefore, is not feasible in many circumstances (22). However, in centers utilizing fertility navigators as part of the management of women of childbearing age newly diagnosed with lymphoma, minimal treatment delays were noted, and delays that did occur did not affect treatment outcomes and survival (23). Citing concerns regarding informed consent of minors, embryo cryopreservation is not permitted for females under age 18 in many facilities. This may pose unique challenges in the management of quality of life in female Hodgkin survivors who were diagnosed prior to age 18. Despite conflicting data as to whether socioeconomic status affects the rate of fertility preservation in women, it is worth noting that fertility preservation is a very expensive process that is often not covered by insurance; therefore, individuals of lower socioeconomic status are less likely to have access to these services (20,22). Some studies also suggest that women with lower levels of education are less likely to broach the issue of fertility preservation with their providers, and, in turn, providers are less likely to broach the topic with these patients (20). In Western societies, individuals are starting families later in life. Additionally, as patients diagnosed with lymphoma at early ages are surviving longer, oncologists should aim to dedicate more time and resources towards the counseling of all patients of reproductive age prior to the initiation of treatment (24).

HIV status

Since the advent of highly active antiretroviral therapy (HAART), the incidence of AIDS-defining malignancies has decreased, but non-AIDS-defining malignancies have now become the second most common cause of death among HIV infected patients. Additionally, HIV infected patients were found to have a decreased survival compared to non-HIV infected patients with the same malignancy (25,26). Possible explanations for this observation could be that HIV infected patients in the US are less likely to have health insurance coverage compared to non-HIV infected patients (26). Additionally, the treatment of HIV infected individuals can be particularly challenging given drug-drug interactions that may exist with HAART and chemotherapy (25). HIV infected patients are often less likely to receive standard of care therapy secondary to the presence of additional comorbidities as well as providers' perception of poor performance status and concern for toxicity among this patient population.

Prior to HAART, NHL such as DLBCL, Burkitt or Burkitt-like lymphoma (BL), primary central nervous system lymphoma (PCNSL), or rare entities that include primary effusion lymphoma (PEL) and plasmablastic lymphoma were more common than HL in HIV infected patients (27). In the era of HAART, the incidence of NHL as decreased, and the incidence of HL among HIV-infected patients has increased up to 20 folds. For both HL and NHL, HIV infected patients present with more advanced disease, higher IPI scores, and worse OS compared to non-HIV infected patients (27-29). Several studies have suggested that one of the major factors contributing to the differences in survival outcomes is treatment delivery (25,26,28). HIV infected patients with HL who were able to be treated with chemotherapy had no difference in outcomes compared to uninfected patients (29). Similar to studies in other malignancies, lack of treatment with chemotherapy for HIV infected patients with HL and NHL was associated with black or Hispanic race, lower socioeconomic status, and lack of insurance coverage (28). These findings are important given that the incidence of new HIV cases in the US are currently highest among blacks (27).

In the past, HIV infected patients have traditionally been excluded from clinical trials; therefore, aside from NHL and anal carcinoma, there are no HIV-specific guidelines for the management of other common malignancies (26). Recently, however, various cooperative groups and regulatory bodies have begun working on efforts to improve access of novel therapeutic agents in clinical trials to patients with HIV. HIV infected patients with adequate immune function should no longer be excluded from clinical trials, including trials with immune checkpoint inhibitors, which are promising agents in various lymphomas and solid tumors currently (28). However, the appropriate care of HIV infected individuals with low CD4 counts and malignancies remains challenging. The coordination of treatment among oncologists, HIV specialists, infectious disease providers, social workers, and pharmacists will hopefully improve the quality of care delivered to HIV infected patients with malignancies (25,28).

Sex and gender minority (SGM)

Lesbian, gay, bisexual, transgender, intersex (LGBTI) individuals account for approximately 3–12% of the population, yet there is a profound paucity of data regarding health outcomes, specifically information regarding the incidence, treatment, and outcomes of lymphoid malignancies in this population (30-33). Most widely used surveys and data collection programs do not capture information regarding sexual orientation and gender identity (34). Recently, sexual orientation and gender identity questions were added to the National Health Institute Survey (35). Regrettably, even in recent years, much of the published research focused on oncology and lymphoma in the LGBTI community is mainly in the context of HIV or other sexually transmitted diseases. Very limited data is available regarding transgender patients, particular those with lymphoid malignancies, and the available data is often in the context of small observational studies (30,32). Data regarding the management of lymphoma in HIV negative sexual minority patients is significantly lacking and is often limited to case reports. As a result of increased association of HIV and lifestyle factors such as smoking and alcohol use noted in various studies, most of what is known or extrapolated to the LGBTI community and malignancy is based older studies of HIV-associated malignancies (36,37). Frisch *et al.* evaluated the association of sexual orientation and malignancy and determined an increased incidence of NHL, as well as anal cancer and Kaposi sarcoma among homosexual men (38). Various studies note an increased incidence of depression in the LGBTI community as a result of stigmatization and discrimination; the presence of depression in general has been noted to increase the risk of malignancy (33,36,39,40). Additionally, compared with cis-gender patients and individuals in heterosexual relationships, LGBTI individuals often have lower rates of insurance coverage (35).

Although there is no universally-accepted, all-inclusive term for this group of patients, more inclusive terminology such as SGM is now being used to represent this group of individuals. Influential bodies such as ASCO and the American Medical Association have recently released statements acknowledging the disparities that exist among SGM individuals (41). SGM patients often face unique psychosocial challenges during both treatment and in survivorship (32,33,42). In particular, these patients are often stigmatized and may face unique challenges with bereavement. Partners report that feelings of loss are often not validated by the medical team. Also, issues of medical decision-making and other legal matters are often complex, which can result in the patient's biological family rather than the patient's "chosen family" or partner making end of life decisions (40,43).

Although considered as a group, the SGM community is very diverse and is faced with the same disparities with respect to racial, cultural, and socioeconomic challenges. Aside from the challenges previously mentioned, transgender patients with lymphoma or any malignancy face additional challenges. For example, malignancy alone is a risk factor for venous thromboembolic disease; however, this risk is further amplified by the use of supplemental hormones being used by many transgender patients. In a recent survey of transgender cancer patients in the United Kingdom, patients diagnosed with thromboembolisms expressed the challenges they face when prioritizing the prevention of additional clots versus the possibility of losing their gender identity by discontinuing hormonal therapy (40). Additionally, given the limited data available to guide the management of transgender patients, particularly from an oncology perspective, optimal screening and prevention measures in this population are not currently known (40,41). Further compounding end of life challenges, many transgender patients do not obtain legal documentation of their preferred gender identity often for fear of the loss of insurance coverage or other challenges from a health-policy perspective. As a result, medical documents including death certificates document the patient's gender at birth rather than their preferred gender (40).

With the many unique challenges faced by this group of individuals, there currently is a significant need for SGM-specific resources that providers can offer to patients and their partners to assist with these challenges (33). The ASCO initiative addresses the need for better patient education, quality improvement and policy changes, availability of SGM-specific support services, as well as the need for increased research. Additionally, the most recent version of Healthy People 2020 included a topic of "LGBT Health" for the first time since the initiative began in 1979 (35). However, these initiatives will be faced with challenges, and efforts will need to be made to ensure adequate training of providers and staff early in their careers.

In May 2016, Section 1557 of the Affordable Care Act (ACA) mandated that health care and health coverage cannot be denied on the basis of sex, including gender identity and sex stereotyping (41,42). Further hindrances to

Table 1 Practice points

Practice points
Racial disparities
Racial minorities
Present at younger ages and with higher risk disease features
Have decreased OS compared to white patients
Prognostic models (FLIPI and IPI scores) have not been validated in racial minority populations
Black patients may be at increased risk of anthracycline-related cardiotoxicity
Gender disparities
The treatment of pregnant women with lymphoma is challenging; outcomes are improved when a multidisciplinary team is involved in the patients' care
Fertility preservation services are significantly underutilized in female lymphoma patients; increased utilization occurs in centers with fertility navigator services
Fertility preservation services are often not covered by insurance
HIV status
HIV positive lymphoma patients
Present with advanced disease and higher risk disease
May face drug-drug interactions with HAART and chemotherapy
Have decreased OS compared to HIV negative patients
Sex and gender minorities
Most data collection programs do not capture sexual orientation and gender identity data
Very limited data exist to guide the treatment of HIV negative SGM patients with lymphoma
SGM patients and partners face unique end of life and bereavement challenges
SGM-specific patient education material is lacking in most institutions

OS, overall survival; FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index, HAART, highly active antiretroviral therapy; SGM, sex and gender minority.

the ACSO and other initiatives may soon come as the future of the ACA is unknown, and the nature of the American health care system in general is currently in flux. As a result, SGM patients are at risk for losing access to insurance coverage, which would negatively impact outcomes and limit access to care (33). Additionally, recent changes to the makeup of the US Supreme Court have many concerned about the future of marriage equality within the US. Various studies have demonstrated that married patients with cancer, including lymphoma and other hematological malignancies, are generally diagnosed at earlier stages and have improved survival compared to unmarried patients (44,45). However, it should be noted that these studies reflect data solely from heterosexual marriages as SGM patients were not included (42). As this population is growing rapidly, more research is needed into the many special circumstances faced by SGM patients in all aspects of cancer care from diagnosis, treatment, survivorship, and bereavement.

Conclusions

With the diversification of the US population and the uncertainty of the state of health care within the US, it is now more important than ever to recognize disparities that exist within the treatment of all patient populations. Although much has been published on racial and gender disparities in general, further questions remain unanswered, such as the optimal use of anthracyclines in black patients and the optimal treatment and timing of treatment for pregnant women with lymphoma. The field has made significant efforts in recent years to improve access to cancer-related treatment for HIV positive patients including efforts currently underway to include HIV positive patients with adequate immune function on clinical trials. However, increasing the access of novel therapeutic agents to HIV positive patients with compromised immune function remains a challenge and an area in need of further research. Additionally, lymphoma patients in the SGM community are faced with unique treatment challenges, but the limited avenues for data collection in this population has been a hindrance to the much-needed research in this population. The recognition of the disparities that exist within lymphoma and oncology as a whole will hopefully lead to policy changes and further exploration into avenues to equalize the treatment and outcomes of all individuals, regardless of race, age, gender, or sexual orientation. *Tables 1* and *2* describe a summary of the above recommendations regarding practice points and future research.

Table 2 Future directions for research

Research directions
Racial disparities
Further evaluation is needed to determine
The application of anthracycline cardiotoxicity prophylaxis guidelines to non-white patients
Prognostic scoring systems applicable to non-white patients
Differences in tumor biology among non-white patients
Gender disparities
Further evaluation is needed to determine
Specific guidelines to manage pregnant patients with lymphoma
Guidelines regarding the use of chemotherapy and radiation treatment in pregnancy
Practice guidelines and health policy changes to increase access of fertility preservation services to female patients with lymphoma
Long-term follow up of individuals exposed in utero to chemotherapy and/or radiation treatments
HIV status
Increase inclusion of HIV positive patients in clinical trials
Increase access to novel treatment options for HIV positive patients
Sex and gender minorities
Further research is needed to
Determine optimal procedures to capture sexual orientation and gender identity data
Determine outcomes in HIV negative SGM patients with lymphoma
Determine healthy policy changes to increase access to care and insurance coverage
Determine optimal management of hormonal therapy in the setting of malignancy-associated thromboembolisms
Increase use of multidisciplinary teams to assist with unique end of life and bereavement challenges in SGM patients
Determine guidelines for SGM-specific screening for secondary malignancies

SGM, sex and gender minority.

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