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Lymphoproliferative Disorders in Young Adults: Review

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Abstract

Lymphoproliferative disorders comprise a heterogeneous group of diseases characterized by uncontrolled production of lymphocytes that cause monoclonal lymphocytosis, lymphadenopathy and bone marrow infiltration. While some Lymphoproliferative disorders such as Hodgkin's Disease and aggressive non- Hodgkin's lymphomas are most common in young adults, other Lymphoproliferative disorders such as indolent non- Hodgkin's lymphomas and plasma cell dyscrasias rarely affect young adults with little sited about their approach and prognosis in this age group. In this review, we highlight some articles and case- series of Lymphoproliferative disorders in young adults and attempt to compare their clinical features and prognosis with those in adults.

Keywords

Lymphoproliferative Disorders; Non- Hodgkin's Lymphoma; Young adults

Introduction

Lymphoproliferative disorders (LPD) comprise a heterogeneous group of diseases characterized by uncontrolled production of lymphocytes (B-lymphocytes, T lymphocytes, and rarely Natural Killers NK) that cause monoclonal lymphocytosis, lymphadenopathy and bone marrow infiltration [1]. Clinicians describe three distinct groups of LPDs; lymphomas, leukemias and monoclonal gammopathies. Phenotypically different cell types characterize these disorders at varying stages of maturation [2]. The disease course, treatment and prognosis vary widely depending on the type of cancer and other individual factors.

Lymphoproliferative disorders affect any age group but shows peculiarities in terms of prevalence of histological sub- types in specific age sub- groups. Some LPDs such as Hodgkin's disease and certain aggressive non- Hodgkin's lymphomas (NHLs) mainly affect adolescents and young adults, thus their course and prognosis in this age group are broadly studies and specified. Conversely, other LPDs such as sub- types of indolent NHLs and monoclonal gammopathies influence young adults very rarely, with paucity of information on their biologic behavior and prognosis in this age group. In this review, we summarize the results of a number of articles and case- series from the past ten years show casing studies of certain rare LPDs in young adults, while attempting to recognize common patterns regarding response to treatment and prognosis compared with those in adults.

Methods

Google search, PubMed, Google scholar were systemically searched for literature from 2010 to May 2020 published in English language using search words lymphoproliferative disorders, non- Hodgkin's lymphoma, plasma cell dyscrasias, young adults. Various combinations of these words are used in the search. Cases- reports, case series, population-based studies, and retrospective case series were all taken into consideration. Articles with only abstracts were excluded.

Follicular lymphoma in young adults

Follicular lymphoma (FL) is the commonest form of indolent NHL. The median age at diagnosis is 60 years. FL is rare under the age of 18 years and accounts for 1-2.5% of lymphomas occurring in that age group and it confers a more favorable clinical outcome than that in adults [3,4]. In contrast, the biologic behavior of FL in young adults has not been well studied. FL in this age group represents 15-20% of all lymphoma diagnoses [5]. In this context, we review the results of a study by Duarte IX et al. [6] conducted in 2013 on a cohort of 200 patients between 19 and 40 years. Patients were evaluated retrospectively with respect to clinical, histological, and genetic features. These were then correlated with clinical outcome.

According to this study, FL in young adults shows many similarities with FL in adults,

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including frequency in anatomic sites, grading distribution and adverse prognostic parameters. The estimated overall survival (OS) was 13 years. A study by Conconi A, et al. [7] was published in 2015, investigating clinical features and outcome of FL in a cohort of 155 young adult patients. While patients younger than 40 years had a lower incidence of elevated LDH and high beta2-microglobulin, bone marrow involvement and bulky lymphadenopathy were more frequent. Younger patients, in comparison with those older than 40, had significantly better overall survival (OS) (a median of 24 years), cause- specific survival (CSS) and progression- free survival (PFS).

Hairy cell leukemia in young adults

Hairy cell leukemia (HCL) is an uncommon chronic B-cell lymphoproliferative disorder in which single courses of cladribine induce high rates of complete responses [8].It predominantly affects middle-aged men with a median age of 50 years. Prior therapeutic trials reported outcomes in patients with a median age of 60 years, while there is limited information about the specific clinical characteristics and outcomes of young patients following cladribine therapy for HCL.

We report the results of a single- institution series study by Rosenberg JD et al. [9] that was published in 2014. This study described the characteristics and outcomes of 88 HCL patients, ≤ 40 years at diagnosis, who were treated with cladribine. The results confirmed prior observations seen in older HCL patients that single courses of cladribine induced very high response rates, the majority of which were complete and durable (88% achieved complete response, 12% achieved partial response), but with a risk of late relapse. Salvage rates with second courses of cladribine in young HCL patients remained high as has been documented in older patients. A small but increased incidence of second primary malignancies was observed in young patients; however, this was not statistically significant. Median overall survival for all patients following the first cladribine course was 231 months, and 251 months from diagnosis. The results from this study indicate that cladribine remains an excellent therapeutic approach for HCL patients, even if diagnosed at a young age. This is the largest report of young HCL patients treated with cladribine. A study by Getta BM et al. [10] published in 2016 compared clinical outcomes and disease complications in 63 patients aged 40 and less at diagnosis with 268 patients > 40 years. There was no difference in the rate of complete remission following initial therapy and estimated 10-year overall survival between the two age groups. However, younger patients required therapy earlier and had a significantly shorter time between first and second therapy (63 *vs*. 145 months; p=0.008) and they required more lines of therapy during follow-up. These results highlight that younger patients with HCL have shorter responses to treatment and require more lines of therapy to maintain disease control, while attaining similar long-term survival.

Chronic lymphocytic leukemia in young adults

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia found in adults in Western countries. It primarily affects the elderly, with the median age of presentation being 72 years [11]. Population- based studies from US and Europe indicate that between 5% and 11% of patients with CLL are <55 years of age at diagnosis [12,13]. The clinical characteristics and outcomes of younger patients (≤ 55 years) with CLL in the era of modern prognostic biomarkers and chemo-immunotherapy are not well understood. Here, we report the results of a study conducted in 2013 by Parikh S A et al. [14] in which baseline characteristics and outcomes of younger patients with CLL who were seen at the Mayo Clinic between 1995 and 2012 were compared with those of patients >55 years.The overall survival of younger patients was compared to that of the age- and sex- matched normal population. The characteristics of 844 newly diagnosed CLL patients with a median age 0f 50 years were compared to those of 2324 patients>55 years. Younger patients were more likely to have Rai stage II disease or I (p<0.0001), be IGHV unmutated (p=0.002) and express ZAP-70 (p=0.009). The time to treatment was shorter in younger patients than those older than 55 years (4.0 years versus 5.2 years; p=0.001) and those ≤ 55 years had longer survival (12.5 years versus 9.5 years; p<0.0001). Adverse prognostic markers appear more common among young patients, although the survival is longer than that of those >55 years. This study is the first comprehensive analysis of younger patients with CLL in the modern era and is the first to report that young CLL patients have a higher prevalence of biologically aggressive disease. Unfortunately, the authors did not provide information on response to treatment and outcome after treatment in younger patients.

Waldenström macroglobulinemia in young adults

Waldenström Macroglobulinemia (WM) is an IgM-associated lymphoplasmacytic lymphoma. It is rare and incurable and is typically diagnosed at a median age of 69 years. Patients younger than 50 years of age account for less than 10% of all WM cases. As such, data for young patients are sparse and the few available studies demonstrate inconsistent findings. In a case- control study by Paludo J et al. [15] that was published in 2016, the authors evaluated outcomes, prognostic features and impact of changing therapies in a large cohort of young symptomatic WM patients (1181 patients) compared to matched older patients seen over the course of the past five decades at Mayo Clinic. Younger patients were more likely to present with adenopathy (p=0.03), and splenomegaly (p=0.004), have higher IgM levels (p=0.0002) and hyperviscosity symptoms (p=0.0003). A retrospective study by Babwah A et al. [16] in 2017 found a similar unexpected finding that 48% of WM patients <40 years presented with symptoms of hyperviscosity at initiation of first line therapy compared to 14% in older WM patients[16]. According to Paludo's study, younger patients had a better 10-year OS than older patients (77% vs. 51%; p=0.0003). No improvement in disease-specific survival (DSS) was noted in younger patients with the use of either front-line rituximab- based therapy compared to non-rituximab based regimens, or front-line chlorambucil-based compared to non-chlorambucil based regimens, which came in contrast to substantial survival gains in the older WM populations in the past 5 decades with those treatment transitions. One study by Vallumsetla N et al. [17] in 2014 of a large cohort of young WM patients (640 patients) seen at Mayo Clinic recommended that nucleoside- analogs (NA) - based therapy was best avoided in this population due to high risk of developing therapy- related myelodysplastic syndrome (t-MDS) or transformed lymphoma compared to patients who received non NA-based therapy (p=0.009).

Multiple myeloma in young adults

Multiple myeloma (MM) is a neoplastic proliferation of plasma cells. It represents 1% of all malignancies and approximately 10% of hematological malignancies. It is considered a malignancy of the elderly, with a median age of 70 years [18]. Very few cases of MM are diagnosed at a younger age, before 40 (approximately 2%) or even under 30 years of age (0.3%) [19,20]. As a result, not much is known about the clinicopathological traits and prognosis in younger patients with MM. Jurczyszyn A et al. [21] conducted a multicenter retrospective study of 52 cases of MM in patients up to 30 years of age that was published in 2018. The age range of patients was 8-30 years. According to this study, 68% of patients had International Scoring System (ISS) of 1; 22% presented with the light chain- only disease, and 48% with elevated serum lactate dehydrogenase (LDH). 85% of patients in this study were treated with novel agents (proteasome inhibitors, immunomodulators), and 62% received front- line autologous stem cell transplantation (ASCT). Overall response rate (ORR) to front line treatment and ASCT were 71% and 90%, respectively. After a follow-up period of 86 months, the median OS was 166 months, with 5-year OS rate of 77%. Those findings suggest that the prognosis in young MM patients may be as good if not better than that in the general population of MM patients.

A case- report of multiple myeloma in a young female presenting with neurological symptoms was reported by Lee M et al. [22] and published in February of 2020. This case entailed a 24-year old young

female who reported diplopia, ataxia, dysphagia and bilateral upper and lower extremity weakness. The patient was eventually diagnosed with MM with multiple extramedullary plasmacytomas. The patient not only failed to respond to initial treatment with CyBorD regimen (cyclophosphamide, bortezomib and dexamethasone) but also progressed acutely while on therapy. Second- line treatments also were ineffective until daratumumab (monoclonal antibody to CD38) was added. This case has multiple atypical aspects including the patient's age, presenting symptoms, and number and location of extramedullary plasmacytomas. Also of note is that despite the patient's high disease burden, her labs were not consistent with the typical features (she had no anemia, hypercalcemia or renal failure) with low beta-2 microglobulin level.

Lastly, we review a case- report of a 19 year old male who was diagnosed with multiple myeloma in our institute in 2019 [23].The patient presented with multiple foci of bone pain. Several osteolytic lesions were evident on simple x-rays and skeletal scintigraphy. The patient was ultimately diagnosed with MM based on bone marrow morphological and immunohistochemical study, along with the presence of monoclonal IgG by immunofixation. The patient achieved remission after first- line therapy with a combination of bortezomib, lenalidomide and dexamethasone. He was later referred to ASCT. This case bares similarities to that by Lee M et al. [21] in that despite the widespread bone involvement, the patient's labs were almost all within the normal range including hemoglobin level, creatinine, LDH, erythrocyte sedimentation rate (ESR) and beta-2 microglobulin.

Conclusion

In the aforementioned Lymphoproliferative disorders, young adults are less commonly affected as an age group, and while they may present atypically and have more adverse prognostic factors compared to older patients, they attain similar survival profiles. Due to the heterogeneity of treatment strategies implemented in the reviewed studies, a comparison of response to treatment between the two age groups cannot be accurately formulated.

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