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Meet the experts

Treatment of mantle cell lymphoma in older adults

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ABSTRACT

Mantle cell lymphoma (MCL) predominantly affects older adults, with a median age at diagnosis of 70 years. A frequently aggressive yet incurable lymphoma, the goal of therapy for MCL is to turn a potentially life-threatening illness into a chronic disease with prolonged periods of remission. Large randomized trial data supports the standard treatment in younger patients of cytarabine-based induction followed by autologous stem cell transplant. Most patients will not be eligible for this intensive approach based on older age, comorbidities, and functional status, making the geriatric assessment an essential step in choosing the appropriate strategy. For these older patients, an increasing number of chemotherapy and non-chemotherapy based therapies are available that allow oncologists to better tailor treatment to the fitness of the patient. We will review treatment options for older patients with MCL in the first line and relapsed/refractory settings, highlighting the available evidence for providing longer progression-free intervals while also minimizing the adverse effects of unduly aggressive treatment.

Contents

1. Introduction

Mantle cell lymphoma (MCL) is a relatively uncommon disease, accounting for only about 5% of non-Hodgkin lymphomas (NHL) [1]. Similar to other NHL, incidence is highest in older adults, with the median age at diagnosis approximately 70 years and 72% of patients diagnosed at age ≥ 65 years [2,3]. Most patients (>80%) present with advanced

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stage disease with involvement of extranodal sites such as the blood, bone marrow, and gastrointestinal tract [4,5]. On pathologic evaluation morphology varies from small to large atypical lymphocytes. Diagnosis requires a combination of flow cytometry (CD20+, CD5+, CD10−, CD23−), fluorescence in-situ hybridization for t(11;14), and immunohistochemical staining for cyclin D1 overexpression [6,7].

The clinical behavior of MCL is typically that of an aggressive lymphoma similar to the more common diffuse large B cell lymphoma (DLBCL), with development of symptoms over weeks to several months and a rapid response after initiation of treatment. An important exception to this is a subset of patients with primarily leukemic, non-nodal disease who may have a more indolent course [8]. Unlike DLBCL, which is curable in about 70% of cases with upfront therapy, MCL is not considered a curable disease [9]. The particular biology that prevents MCL from being cured despite its aggressive behavior is still being elucidated, involving interactions within the tumor microenvironment that protect a small population of lymphoma cells from chemotherapy-induced cytotoxicity [10]. The goal of therapy is extended disease-free survival, with tolerable retreatment at time of relapse.

Although historically associated with a poor prognosis and survival of only several years, MCL outcomes have improved over the last several decades. In a cohort of patients from 1996 to 2004, median overall survival (OS) approached 5 years [11]. Survival has continued to improve, as younger patients benefit from large studies on intensive therapy followed by autologous stem cell transplantation (ASCT) [12,13]. For the geriatric population, treatment options have expanded to include both chemotherapy and non-chemotherapy regimens, allowing for better tailoring of treatment to the individual patient. In this review we will focus on older patients not eligible for ASCT, conceptually forming three groups: “fit” patients eligible for moderately intensive chemotherapy-based first-line therapy, “unfit” patients more appropriate for non-intensive initial therapy, and those with relapsed or refractory disease (Fig. 1).

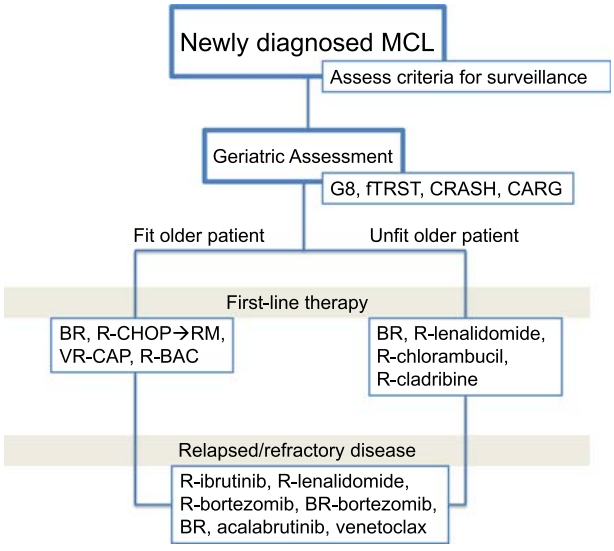

Fig. 1. For the older patient diagnosed with MCL, geriatric assessment prior to selection of treatment is required. Patients qualified as fit are candidates for moderately intensive chemotherapy-based regimens, with bendamustine-rituximab (BR) the preferred choice. The unfit older adult is best treated with less intensive regimens. For relapsed/refractory disease, an increasing number of options are available that are appropriate for both fit and unfit older adults. Of note, venetoclax is not FDA approved for MCL. fTRST = Flemish version of the Triage Risk Screening Tool. CRASH = Chemotherapy Risk Assessment for High-Age patients. CARG = Cancer and Aging Research Group model. R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone. RM = rituximab maintenance. VR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone. R-BAC = rituximab, bendamustine, low-dose cytarabine. R = rituximab.

2. Geriatric Assessment

Prior to deciding on a treatment plan for any cancer patient, evaluating level of fitness is necessary to predict how therapy will be tolerated. The standard method of assigning an Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance status is often insufficient in the geriatric population. For example, a large study revealed physician-rated Karnofsky performance status in older adults is not predictive of treatment toxicity [14]. When compared to a formal geriatric evaluation, the clinical judgment of oncologists frequently results in an overestimation of patients' level of fitness [15]. A more accurate fitness assessment provided by the geriatric evaluation is predictive of treatment outcomes, as shown in elderly patients with DLBCL [16,17].

Various methods for assessing fitness in geriatric patients in the context of mantle cell lymphoma were recently reviewed in detail [18]. A comprehensive geriatric assessment (CGA) completed by a geriatrician provides the most thorough evaluation [19]. From a practical standpoint however, CGA is unfamiliar to most oncologists, and having every older patient with cancer undergo pre-treatment consultation with a geriatrician is not feasible.

A number of screening tools are available for a more concise evaluation of fitness level and identification of patients who will most benefit from a comprehensive evaluation [20]. A comparison of the G8 and Flemish version of the Triage Risk Screening Tool (fTRST) in cancer patients ≥70 years old found both are predictive of functional decline and overall survival [21]. The G8 screening tool in particular is well validated in older patients with cancer and has recently been updated [22].

A foremost concern for oncologists caring for patients with cancer is the risk of treatment-related toxicity. Two prediction tools are available that incorporate chemotherapy and patient-specific factors to help estimate this risk for older adults. The Chemotherapy Risk Assessment for High-Age patients (CRASH) score stratifies patients into four groups, with risk of severe toxicity ranging from 50% to 79% [23]. The Cancer and Aging Research Group (CARG) model predicts grade 3–5 chemotherapy toxicity, from 37% to 70% depending on risk group [24]. Both of these prediction tools are externally validated and have online calculators available.

3. Observation Versus Immediate Treatment

Most patients with MCL require treatment at the time of diagnosis due to the aggressive clinical course. For a carefully selected minority of patients, a period of observation may be appropriate. A single-center retrospective study of 97 patients evaluated the safety of this strategy [25]. Based on clinician judgment, 31 patients were initially observed, with the other 66 patients receiving early treatment. Median survival for the observation group was not reached, compared to 64 months for those initially treated ($p = 0.004$). The median time to treatment in the observation group was 12 months. Factors correlating with patient selection for observation included better performance status, limited stage disease, and lower International Prognostic Index (IPI) score, suggesting more indolent disease. This strategy of observation for indolent MCL has since been confirmed in additional studies [26–28].

Recent studies on the molecular pathogenesis of MCL illustrate why not all cases follow an aggressive course. Two distinct subtypes of MCL with varied clinical behavior have emerged [8]. The first subtype has an unmutated immunoglobulin heavy-chain variable region (IGHV) and genetic instability, blastic or pleomorphic morphology, predominantly nodal and extranodal disease, and an aggressive course. The second subtype has mutated IGHV, genetic stability, and presents primarily as leukemic, non-nodal disease with a more indolent disease course [29,30].

The MCL international prognostic index (MIPI) utilizes four factors – age, performance status, lactate dehydrogenase (LDH), and white blood cell count (WBC) – to place patients into risk groups based on median overall survival prior to initiation of therapy [31]. The addition of Ki-

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