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Mantle cell lymphoma: The promise of new treatment options

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Abstract

Though the expected overall survival (OS) for mantle cell lymphoma (MCL) has doubled in the last 30 years it is still in the range of only 4–5 years. Despite high response rates with current first-line treatments, most patients eventually relapse and become typically chemoresistant, leading to very poor outcome in the relapsed setting. Here, we summarize the clinical characteristics of MCL and frontline strategies used in MCL, and review a number of novel options that are currently being investigated in an effort to extend survival outcomes for this difficult-to-treat patient population. Among these novel options figure cytotoxics (bendamustine, cladribine), new biologicals/small molecules such as proteasome inhibitors (bortezomib 1st drug approved in the USA for MCL), mTOR inhibitors with temsirolimus (1st drug approved in EU for MCL), CDK inhibitors (flavopiridol); IMiDs (thalidomide, lenalidomide); HDAC inhibitors, Bcl-2 inhibitors and second or third

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generation monoclonal antibodies or immunotoxins. The panel of novel drugs approved or being tested offers new opportunities in the management of MCL from combination in the frontline setting (e.g. bortezomib-R-chemo) to post-induction strategies such as consolidation (e.g. radioimmunotherapy, bortezomib) or maintenance therapy (e.g. rituximab, lenalidomide).

Keywords: Mantle cell lymphoma; Non-Hodgkin's lymphoma; Rituximab; Bortezomib; Flavopiridol; Bendamustine; Temsirolimus; Lenalidomide

1. Introduction

Mantle cell lymphoma (MCL) is a lymphoma subtype that accounts for 5–7% of non-Hodgkin's lymphomas (NHL). Although the expected overall survival (OS) for MCL has doubled over the last 3 decades [1], it currently remains in the range of only 4–5 years. Though MCL patients respond to initial therapy, a continuous pattern of relapse follows with common subsequent chemoresistance and very poor outcome. With the exception of rare patients who enjoy long term disease-free survival after non-myeloablative allogeneic stem cell transplantation (SCT), there is no curative therapy defined for MCL, which carries one of the worst prognoses among B-cell lymphomas [2,3], especially in the relapse setting.

Modern treatment options consisting of anthracycline-based, rituximab-containing chemotherapy combinations and high dose chemotherapy (HDT)/myeloablative consolidation with autologous stem cell transplantation (ASCT) regimens have improved overall response rates (ORR), complete response (CR) rates, progression-free survival (PFS) as well as time to treatment failure (TTF) [4,5]. When added to first-line, anthracycline-based chemotherapy, rituximab improved ORR and TTF, but provided no benefit in either PFS or overall survival (OS). Only about one-quarter of patients remained progression-free after 2 years following R-CHOP ([rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone]) [6]. Although chemotherapy regimens containing rituximab followed by ASCT, as well as dose-intense regimens (R-HyperCVAD) ([rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone]), have improved clinical outcomes (extending PFS) relative to standard chemotherapy, patients continue to relapse and whether such approaches have a beneficial impact on OS is still debated [7,8].

Following relapse, median life expectancy for a patient with MCL declines to 1–2 years [9], and there are few effective treatment options available. Bortezomib and temsirolimus are currently the only drugs approved by the United States Food and Drug Administration (USFDA) and European Medicines Agency (EMEA), respectively, for the treatment of relapsed or refractory MCL. This paper will briefly summarize the clinical characteristics of MCL and review the available data on new treatment options as well as strategies that are currently being explored in an effort to extend survival outcomes for this difficult-to-treat patient population.

2. Search strategy and selection criteria

Data for this review were identified by searches of EMBASE, PubMed, and references from relevant articles using the search term "mantle cell lymphoma". Abstracts and reports from meetings were included only when they related directly to previously published work. Only papers published in English between 1995 and 2009 were included.

3. Diagnosis

Patients with MCL usually present with advanced disease [3,9], though less than one-third have B symptoms at presentation. Typical clinical characteristics of MCL patients include a median age at diagnosis of >60 years, a male predominance, advanced disease (~70% Ann Arbor stage IV), and extranodal involvement, including bone marrow, blood, spleen, liver, and gastrointestinal tract [10–12,3,9]. Gastrointestinal tract involvement can vary from regular polyps to extensive polyposis coli or normal mucosa, but random biopsies have been shown to be positive in approximately 90% of patients at baseline (hence not indicated as part of initial work but to be considered for restaging on therapy) [13]. Histologically, MCL is characterized by neoplastic expansion of the mantle zone surrounding lymph node germinal centers (antigen naïve cell) and a homogeneous population of small- to medium-sized lymphocytes with irregular nuclei, condensed chromatin, inconspicuous nucleoli, and scant cytoplasm (Fig. 1) [10–12,14,15]. The histological pattern may be diffuse, nodular, or a combination of the two mixed histologies, while the mantle-zone variant is rare and more indolent [11]. At the cytological level, variants include classic small cells subtype, lymphoblastoid and pleiomorphic subtypes with clearly some overlap, illustrating the fact that MCL may encompass a spectrum of diseases [16], which is also suggested by molecular profiling studies [16].

The classical immunophenotype of MCL reflects a mature B cell (CD19+, CD20+, CD22+, CD79a+) and is usually CD5+, CD43+, while negative for CD10, CD23 and Bcl-6 [10–12,17]. In some rare cases, however, MCL may be CD5–or CD23+ [17]. The t(11;14)(q13;q32) translocation is the hallmark cytogenetic abnormality of MCL. This translocation places the *cyclin D1* gene, which regulates progression through the G1 checkpoint of the cell cycle, under the transcriptional control of the immunoglobulin (Ig) heavy chain gene enhancer region on chromosome 14. This results in a significant overexpression of *cyclin D1*, which is not nor-