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Reviews

Therapeutic Advances in the Treatment of Primary Plasma Cell Leukemia: A Focus on Hematopoietic Cell Transplantation

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A B S T R A C T

Primary plasma cell leukemia (pPCL) is an uncommon but aggressive plasma cell malignancy associated with frequent extramedullary involvement, high-risk cytogenetic abnormalities, and frequent organ dysfunction, ultimately resulting in poor prognosis. Here we review recent advances in our understanding of the molecular and biological aspects of PCL and summarize therapeutic progress occurring over the past 2 decades. pPCL is distinguished from secondary PCL arising from multiple myeloma. The molecular and immunophenotypic changes of pPCL are often distinct from those seen in secondary PCL and multiple myeloma. The availability of novel agents (ie, proteasome inhibitors and immunomodulatory agents) and the increasing use of hematopoietic cell transplantation strategies have resulted in better outcomes, although long-term survival remains poor. Development of complex treatment algorithms that combine novel agents as induction therapy, as part of conditioning regimens for hematopoietic cell transplantation (autologous or allogeneic), or as post-transplantation remission strategies are logical and may translate into improved survival in patients with PCL.

INTRODUCTION

Plasma cell leukemia (PCL) accounts for 0.3% of cases of acute leukemia, up to 4% of multiple myeloma (MM)-associated presentations, and 12% of cases of MM with high tumor burden [1,2], and most commonly presents with circulating plasma cells and an aggressive clinical course. The definition of PCL, as established by Kyle et al. [3], requires the presence of an absolute plasma cell count >2000/μL or >20% plasma cells in peripheral WBCs [4]. The disease may be primary (pPCL), presenting *de novo*, or may evolve during the course of relapsed or progressive MM, termed secondary (sPCL) [5,6]. The overall prognosis of PCL is generally poor compared with that of MM. Notwithstanding that both pPCL and sPCL might share similar biological and clinical courses, sPCL generally represents a more aggressive and fulminant plasma cell disorder, with a median survival of a few months (1.3 months for sPCL versus 11.1 months for pPCL) [7].

The overall prognosis of pPCL is also poor, with reported survival expectancy of less than 1 year in the majority of cases [1,2], considerably shorter than that of patients with MM with a high tumor burden [1]. Moreover, pPCL is associated with early mortality [8]. The optimal front-line therapy for patients with pPCL remains undefined; novel agents such as bortezomib appear to be active against PCL, but data are still largely limited to institutional case series and case reports [1,2,9]. Hematopoietic cell transplantation (HCT), both autologous and allogeneic, has proven feasible based on small series and retrospective registry analysis; however, prospective randomized controlled data are lacking.

Here we provide a comprehensive review that evaluates the current understanding of the biological and genetic aspects of PCL, as well as recent therapeutic advances including conventional chemotherapy, novel agents, and autologous and allogeneic HCT. A suggested treatment strategy is discussed, and future therapeutic options are explored.

LITERATURE SEARCH STRATEGY

A comprehensive medical literature search was conducted using PubMed (1966 to November 23, 2012), with the following search strategy: "Leukemia, Plasma Cell" (MeSH). A total of 774 publications were identified, with 394 deemed relevant to PCL and 380 not relevant to PCL. Relevant articles focusing on chemotherapy, autologous HCT, and allogeneic HCT were selected. For the purpose of this review, single case reports were excluded. Findings from these selected articles are summarized herein.

CHARACTERISTICS OF PCL

Clinical

The median age at diagnosis of PCL is 53-57 years, at least a decade younger than the median age at diagnosis of MM [1,7,9,10]. A recent report based on the Surveillance, Epidemiology, and End Results database identified at total of 291

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patients with PCL between 1973 and 2004, with a median age of 67 years (range, 19 to 98 years) [11]. However, that analysis did not distinguish pPCL from sPCL, and literature on chemotherapy and HCT may have an inherent selection bias for reporting results of younger patients with good performance status. The reported percentage of pPCL cases in males varies from 38% to 60% [2,7,9,12].

Clinically, patients with PCL may present with extramedullary involvement (14%-23%), hepatomegaly (7%-73%), splenomegaly (18%-53%), lymphadenopathy (3%-40%), elevated lactate dehydrogenase, hypercalcemia, hypoalbuminemia, and thrombocytopenia (median platelet count, 62-123 $\times$ 10^9/L) [1-3,7,9,13]. Renal impairment is common (serum creatinine $>$2 mg/dL), and is seen in 33%-53% of cases [2,7,13]. Leptomeningeal infiltration has been reported. Interestingly, skeletal lytic lesions are less common in pPCL (35%-67%) compared with sPCL or MM (79%-81%) [2,7,9,10,13].

Genetic and Molecular

Cytogenetic changes, including hypodiploidy, pseudodiploidy, complex karyotype, and monosomy 13, are more common in PCL than in MM [2,8,14]. Deletion of 13q by fluorescence *in situ* hybridization can be detected in up to 85% of cases of pPCL [2,7]. Deletions or mutation of p53 conferring adverse prognosis has been reported more frequently in PCL compared with MM (20%-56% in pPCL and 83% in sPCL versus 10%-15% in MM) [7,15-18]. Chromosome 1 abnormalities are often seen in association with PCL [19]. Amplification of 1q21 and deletion 1p21 are more common in PCL (46%-67% and 21%-44%, respectively) than in MM (30%-43% and 20%-36%, respectively), contributing to the worse prognosis in PCL [16-18,20-22]. Chang et al. [20] reported a significantly greater increase in amplification of the cyclin-dependent kinase regulatory subunit 1 (*CKS1B*) gene in patients with PCL (62%) compared with patients with MM (relapsed, 52%; newly diagnosed, 36%; 0% in cases of monoclonal gammopathy of undetermined significance) ($P < .001$).

Interestingly, immunoglobulin heavy chain (IgH) translocations in patients with primary PCL selectively involve 11q13 (cyclin D1 [*CCND1*]), likely supporting a key pathogenic role in such cases [7]. On the other hand, multiple partner oncogenes appear to be involved in the development of sPCL, including 11q13, 4p16 (fibroblast growth factor receptor 3 [*FGFR3*]/multiple myeloma SET domain [*MMSET*]), and 16q23 (macrophage activating factor [*MAF*]), among others [7].

The progressive decline in CD38 expression from normal plasma cells to monoclonal gammopathy to MM and then to PCL likely indicates a dedifferentiated state in PCL [22]. Overexpression of CD27 may play a role in the biology of PCL through activation of the nuclear factor-κB pathway and exertion of antiapoptotic properties [23,24].

Hallmarks of PCL are extramedullary invasion, the ability to recirculate in blood, and expansion of plasma cells independent of the putative protective bone marrow microenvironment niche. One hypothesis associates lower expression of CD56 (which is typically expressed in malignant plasma cells), neuronal cell adhesion molecule, and leukocyte function-associated antigen 1 on clonal plasma cells with the tendency to form nodular plasma cell aggregates, and hence the leukemic presentation [2,25]. Elevated levels of death receptor CD95 have been reported in patients with PCL [22]. Up-regulation and rearrangements of the Myc proto-oncogene are associated with worse prognosis in pPCL [7,17,26]. Activating mutations of *NRAS* and *KRAS* are seen more frequently in pPCL compared to MM [7,27]. In addition, gene expression profiling of pPCL appears to show a distinct clustering, and pPCL may be a subentity of MM based on gene expression profiling findings [28].

THERAPEUTIC MODALITIES

Conventional and Combination Chemotherapy

Before embarking on the treatment of PCL, it is important to rule out benign reactive plasmacytosis, which is commonly associated with infections and rheumatologic conditions [29]. Reactive plasmacytosis may mimic PCL but is polyclonal in nature; careful immunophenotyping with flow cytometry is essential to differentiate the 2 conditions [30].

Data are limited on therapeutic options for patients with PCL, owing in part to early mortality and lack of prospective trials specific for patients with PCL. Conventional regimens using standard-dose alkylator-based therapy without novel agents have provided disappointing results [1]. A series of 12 patients with pPCL treated with melphalan plus prednisone had a median survival of only 2-3 months [2].

Multiagent systemic conventional chemotherapy regimens may offer prolonged survival. One study reported a median survival of 18 months in patients treated with combination chemotherapy (ie, vincristine, cyclophosphamide, melphalan and prednisone/vincristine; bleomycin, adriamycin, and prednisone), compared with only 3 months in those treated with melphalan plus prednisone [2]. Another report indicated that intermediate dose melphalan (80 mg/m^2 orally per cycle with dexamethasone) was associated with better survival than a vincristine, doxorubicin, and dexamethasone regimen in patients with pPCL [12].

The availability of novel agents, including proteasome inhibitors and immunomodulatory agents, has improved outcomes in patients with PCL [31]. A retrospective study of 128 patients with PCL by Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) between 2000 and 2008 suggested improved survival after bortezomib or thalidomide therapy [31]. Several case reports and small case series have demonstrated a benefit of bortezomib, alone and in combination with other agents, in patients with PCL [32-34]. Selected studies on novel agents in treatment of PCL are summarized in Table 1.

Thalidomide as a single agent does not appear to be sufficiently efficacious for treating PCL [35]. The use of thalidomide as a maintenance option after autologous HCT had been explored [36-38]; however, this option may be obsolete today, considering lenalidomide's better efficacy and tolerability. Combination chemotherapy incorporating thalidomide may demonstrate enhanced activity [39,40], but the data are not based on randomized controlled studies.

GIMEMA also reported a retrospective analysis of 29 patients with pPCL who received front-line bortezomib-containing regimens between 2006 and 2010 [41]. The overall response rate was 79%, with 38% very good partial response (VGPR) or better, and renal function improved in 10 of the 11 patients with renal impairment. A 2-year progression-free survival (PFS) of 40% and 2-year overall survival (OS) of 55% were reported. The data suggested that a bortezomib-based induction regimen might be associated with better long-term outcomes after autologous HCT consolidation [41]. Other studies have also reported improved survival with bortezomib-containing regimens [31,42,43]; however, the experience from the Arkansas group and the Intergroupe Francophone de Myéloma did not