Plasma cell leukemia: update on biology and therapy

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Running title: Update on Plasma Cell Leukemia

Keywords: PCL, Plasma cell leukemia, primary PCL, secondary PCL, autoulogous stem cell transplantation, novel agents.

Abstract

Plasma cell leukemia (PCL) is a rare, but very aggressive, plasma cell dyscrasia, representing a distinct clinicopathological entity as compared with MM, with peculiar biological and clinical features. A hundred times rarer than multiple myeloma (MM), the disease course is characterized by short remissions and poor survival. PCL is defined by an increased percentage (>20%) and absolute number (>$2x10^9$/l) of plasma cells in the peripheral blood. PCL is defined as "primary" when peripheral plasmacytosis is detected at diagnosis, "secondary" when leukemization occurs in a patient with pre-existing MM. Novel agents have revolutionized the outcomes of MM patients and have been introduced also for the treatment of PCL. Here we provide an update on biology and treatment options for PCL.

INTRODUCTION

Plasma cell leukemia (PCL) is the most aggressive variant of clonal plasma cell dyscrasias[1,2]. The incidence of this uncommon hematologic malignancy in Europe is about 0.04 cases per 100,000 persons per year[3]. The diagnostic definition of PCL is based on Kyle's criteria[4], requiring both an absolute plasma cell count greater than $2x10^9$/l in peripheral blood and more than 20% circulating clonal plasma cells. However, this cut-off is arbitrary, it has not been prospectively validated and it may underestimate the frequency of PCL. Recent reports suggest that a lower degree of peripheral plasmacytosis could be sufficient to define this disease entity along with the associated poor clinical outcome. In 2 independent series of MM patients treated with novel agents-containing regimens [5,6], circulating plasma cell levels as low as 1-2% predicted a survival similar to classically defined plasma cell leukemia. These findings need to be validated in larger cohorts, and it is not clear if a low degree of plasmocytosis represents a risk factor in MM or defines PCL. PCL is defined as primary (pPCL) when the leukemic phase is already present at diagnosis, while secondary PCL (sPCL) represents a leukemic progression of relapsed and/or refractory multiple myeloma (MM) (Table I). Approximately 60% of PCL patients have pPCL, while sPCL represents the remaining 40% of cases [7].

CLINICAL FEATURES

Compared to MM, pPCL has distinct clinical and laboratory features[8–11]. The median age at diagnosis of pPCL ranges between 52 and 65 years, about 10 years earlier than the median age of MM and sPCL onset[12]. Clinical presentation is more aggressive than MM and due to the leukemic nature of the disease, the diffusion to

extramedullary sites (Lymph nodes, liver, spleen, pleura, CNS, soft tissues) is relatively frequent (up to 20%)[13,14]. Tumour burden is generally high and patients usually presents with symptoms due to anemia (haemoglobin<8.5 g/dl 54% vs 31% in MM), thrombocytopenia (Platelets<100x10^9/l 48% vs 9% in MM) and hypercalcemia (serum calcium≥11 mg/dl 48% vs 20% in MM) at diagnosis. High rates of renal insufficiency (serum creatinine≥2 mg/dl 44% vs 21% in MM), elevated β2-microglobulin (≥6 mg/l 65% vs 27% in MM) and elevated lactate dehydrogenase (LDH) levels (≥460 U/l 48% vs 9% in MM) are also typical of pPCL[13]. Conversely, osteolytic lesions are less common in pPCL (35% of patients) compared to MM (81% of patients) and sPCL (53% of patients)[12]. Regarding the type of monoclonal immunoglobulin heavy chain in pPCL patients, the most common is IgG (30%), followed by IgA, IgD and IgE. Strikingly, 35-40% of patients produce light chains only, and 8% are non-secretors [12]. Survival data on pPCL in descriptive studies before the era of novel agents have demonstrated a median overall survival (OS) of less than 12 months[2,13,15]. Gonsalves and collegues[16] reviewed survival data of 445 pPCL patients diagnosed in the USA between 1973 and 2009 registered in the Surveillance, Epidemiology, and End Results (SEER) database. Patients were divided in 4 groups based on the period of diagnosis in order to find out whether the introduction of autologous stem cell transplantation (ASCT) and novel agents into clinical practice (respectively 1995 and 2006) have had an impact on survival. Diagnosis of pPCL during 2006-2009 compared to diagnosis prior to 2006 was associated with an improved OS (12 months vs 5 months) in multivariable analysis. However SEER database does not contain information about treatment, therefore caution is needed, and no definitive conclusions can be drawn.

MM progression to sPCL is associated with end stage disease and a fulminant clinical course. The median time from MM diagnosis to leukemic progression is approximately 20-22 months, earlier than the median survival of MM patients, suggesting that a fraction of patients is more prone to leukemic progression[17].

sPCL patients are heavily pre-treated and usually refractory to all available drugs, with a median OS of only one month[12]. Best supportive care and effective palliation should be offered to the patient, especially when therapeutic failure occurs and further therapeutic options are exhausted.

BIOLOGY OF PLASMA CELL LEUKEMIA

From a biological point of view, MM, pPCL and sPCL are profoundly different; pPCL represents a distinct entity from the beginning, while sPCL is characterized by a multistep accumulation of adverse biological features in patients with advanced relapsed and/or refractory MM. *Figure 1* summarizes the main alterations in pPCL and sPCL.

PCL cells, unlike MM cells, are poorly dependent on the bone marrow (BM) microenvironment for their growth and survival. The neoplastic plasma cells are more prone to enter the blood stream due to changes in expression of adhesion molecules[18], chemokine receptors[19] and the presence of molecular aberrations promoting tumor growth outside the BM, inhibition of apoptosis and escape from immune surveillance[20]. The genomic characterization of PCL has been evaluated with many techniques, from conventional karyotyping to high-throughput molecular

biology. Even though PCL cells share some of the genetic lesions found in MM, several specific features can be found.

IMMUNOPHENOTYPE

While plasma cells' markers CD38 and CD138 are expressed at the same extent in PCL and MM, PCL cells express more often CD20, CD23, CD44, CD45 and less often CD9, CD56, CD71, CD117, HLA-DR compared to MM[9,11,20,21]. PPCL and sPCL share a similar immunophenotype, except for CD28 that is more frequently expressed in sPCL[21]. Consistently, CD28 antigen expression on MM plasma cells is associated with plasma cell proliferation, disease progression, chemotherapeutic resistance and a poor outcome[22,23].

CYTOGENETICS AND GENETIC ABERRATIONS

Cytogenetic alterations are more frequent in PCL than in MM[24]. The accurate evaluation of the frequency of each type of aberration is difficult because of the small number of patients included in the available studies and the lack of a standardized method of detection. Moreover the association of each aberration with PCL prognosis could be misleading because of treatment bias and because PCL is associated with poor prognosis "per se". The karyotype of PCL cells is more often non-hyperdiploid compared to MM (70-90% vs 40% respectively)[25,26]. Chromosomal translocations involving immunoglobulin heavy-chain (IgH) locus are usually observed both in pPCL and sPCL (87% and 82% respectively). PPCL cells are frequently (71%) and typically positive for t(11;14)[12], where the IgH locus translocation's partner is Cyclin D1, supporting an important role of this gene in the disease's biology. Conversely,

although many cases of sPCL are also positive for t(11;14) (23%), t(4;14) and t(14;16) are slightly more frequent (both 16% in sPCL cases)[12]. The most frequent copy-number alteration observed in pPCL cases is 13q deletion (85%), at higher levels than MM (54%) and sPCL (67%)[12,27]. Moreover, compared to MM, both pPCL and sPCL show an increased frequency of 17p deletion (37% in PCL vs 11% in MM), 1p21 deletion (33% in PCL vs 18% in MM) and 1q21 amplifications (51% in PCL vs 34% in MM)[27]. In particular 17p deletion complemented by functionally relevant TP53 coding mutations lead to an allelic TP53 inactivation in 56% of pPCL and 83% of sPCL cases[9]. Interestingly, 17p deletion as well as TP53 coding mutations are rare and occur late in MM history[28]. Beyond direct genetic damage, a functional inactivation of TP53 gene can be achieved through overexpression of negative regulatory elements, such as mouse double minute 2 homolog (MDM2), or by decreased activity of CDKN2A (p14ARF), a negative regulator of MDM2[29,30]. TP53 damage or inactivation can lead to a diminished surveillance of genome stability of PCL cells. In this unstable genomic status, mutations in oncogenes are more likely to occur. Indeed functionally activating mutations of KRAS or NRAS are found in 27% of pPCL and 15% of sPCL[12]. In MM the prevalence of these mutations is comparable to sPCL cases, suggesting that KRAS or NRAS activation is not associated with secondary leukemization[10]. Concerning another important oncogene, many types of MYC locus abnormalities (Chromosome 8q24) have been identified in PCL. Rearrangements, amplifications or translocations were found by fluorescent in situ hybridization (FISH) in about a half of pPCL and sPCL cases[12]. Combining FISH and array comparative genomic hybridization (aCGH) technique, Checchio et al evidenced structural and numerical abnormalities of 8q24 region, confirming that MYC dysregulation by complex mechanisms is one of the major

molecular events in the oncogenesis of PCL[26]. Quantitative polymerase chain reaction (PCR) showed that these alterations led to MYC overexpression, with varying levels depending on the type of genomic abnormality involved[26].

HIGH THROUGHPUT ANALYSIS OF pPCL

In the last few years, high throughput technologies have increased our knowledge about the genetic landscape of plasma cell dyscrasias. A total of 5 published studies exploited high throughput technologies in pPCL[31] (Table II). Gene expression profiling (GEP) was used in 3 trials to study the trascriptome of pPCL. Usmani and colleagues studied pPCL patients treated with Total therapy protocols[32]. GEP revealed a signature of 203 genes separating pPCL from non-pPCL cases. These genes belong predominantly to the lipid-metabolism pathway and some of them are normally expressed in monocytes and macrophages, raising the possibility that myeloid differentiation of myeloma cells may be responsible for leukemic presentation. Mosca et al. combined single nucleotide polymorphism (SNP) array and FISH data with the corresponding transcriptome profiles of 23 pPCL patients enrolled in a phase II prospective trial[33]. This approach allows the evaluation of the influence of allelic imbalances in PCL cells' transcriptional expression. Interestingly, transcriptional modulation of 382 genes mapped within altered copy numbers regions. In particular, genes involved in methyltransferase activity, protein transport, translation and synthesis were positively modulated while genes involved in RNA splicing, transcription, protein catabolic process and apoptosis were downregulated in the genomic regions with copy number alterations. Todoerti and colleagues[34] assessed 55 MM and 21 pPCL patients included in the same prospective trial using GEP analysis,

and they correlated their findings with the study outcome endpoints. The expression fingerprint of pPCL and MM samples was greatly affected by the main IgH locus translocation, but a 503-gene signature was able to distinguish pPCL from MM. Only 15% of the signature overlaps with Usmani's findings (see above), including genes involved in cytoskeleton functions, Rho protein signalling, and NF-κB pathway. They also detected a 27 gene-signature identifying pPCL patients with the poorest survival.

Coding mRNAs measured in GEP are targeted and regulated by short non-coding RNAs called microRNAs (miRNA). A miRNA expression profiling through microarray analysis was performed by Lionetti et al[35] in pPCL patients. MiRNAs differentially expressed in pPCL compared to MM may play a role in the development of the disease, the expression levels of 4 miRNA (miR-497, miR-106b, miR-181a0, and miR-181b) correlated with treatment response, and 4 (miR-92a, miR-330-3p, miR-22, and miR-146a) with clinical outcome.

Today the only study providing next-generation sequencing data about the mutational profile of pPCL cases was performed by Cifola and collegues[36] through whole exome sequencing. This technique allows the detection of somatic mutations in coding DNA of the PCL cell genome. They analyzed 12 pPCL cases identifying 1,928 coding somatic non-silent variants on 1,643 genes, with a mean of 166 variants per sample. The recurrently mutated genes were very rare and only 14 genes with a potential driver role in pPCL were identified. These genes are involved in cell-matrix adhesion and membrane organization (SPTB, CELA1), cell cycle and apoptosis (CIDEC), genome stability (KIF2B), RNA binding and degradation (DIS3, RPL17), and protein folding (CMYA5).

LONGITUDINAL TRACKING OF sPCL

Regarding sPCL, the most interesting studies longitudinally tracked myeloma cell genome from diagnosis to leukemization[37,38]. The complexity of malignant plasma cell genome increases over time, especially in the presence of cytogenetically-defined high risk disease. Clonal heterogeneity is already present at diagnosis and clonal composition is affected by time and treatment. As an example two cases of rapid sPCL progression reported by Mangiacavalli and collegues[17] had a high percentage of myeloma cells with chromosome 17p13 alterations at diagnosis with a further expansion at the time of secondary leukemization. Egan et al[37] analyzed a case of MM with t(4;14) progressed to sPCL using Whole Genome Sequencing (WGS). Somatic mutations affecting 5 genes (RB1, TNN, TUBB8, ZKSCAN3 and ZNF521) were found only in sPCL stage suggesting an association with leukemization in this patient. Unfortunately, this kind of analysis was only done in sporadic sPCL cases and no conclusion can be drawn without larger studies.

TREATMENT OPTIONS FOR PLASMA CELL LEUKEMIA

The investigation of newer drugs in prospective clinical trials has been limited in PCL due to the low incidence of this disease. Therefore, data about safety and efficacy of various drugs and combinations in PCL patients mainly come from heterogeneous retrospective trials.

The reported OS of patients treated with alkylating agents and corticosteroids only was approximately 4 months[2,13]. Furthermore, the combination of different

conventional chemotherapeutic agents (vincristine and doxorubicin) in multi-drug regimens did not significantly improve responses and survival[39–41].

NOVEL AGENTS

The introduction of novel agents, such as the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor bortezomib, has revolutionized the treatment landscape of MM and dramatically improved survival of MM patients[42].

Data from both retrospective and prospective studies seem to suggest a survival improvement for PCL patients treated with new drugs. Yet, results are conflicting and differently from MM, no clear advantage has been observed in PCL patients. (Table III)

Thalidomide

Limited data are available about thalidomide for the treatment of PCL. In case reports with small number of patients, single agent thalidomide did not show any meaningful activity in patients with both pPCL and sPCL[43]. Better results were observed when thalidomide was combined with conventional chemotherapy[44,45]. Because of the development of newer and more efficacious agents against extramedullary plasma cell dyscrasias, thalidomide fell soon into disuse in this setting.

Lenalidomide

In initial reports, lenalidomide showed promising activity in both pPCL and sPCL[46–48]. Lenalidomide is the first novel agent tested in a prospective trial in patients with pPCL.

The Italian GIMEMA group performed a phase II trial to test safety and efficacy of lenalidomide in combination with dexamethasone (Rd).[49] Between 2009 and 2011 a total of 23 patients with newly diagnosed pPCL were enrolled in the trial. Treatment consisted of 4 cycles of Rd induction, followed by stem cell transplantation in eligible patients, and lenalidomide maintenance in transplant-ineligible patients. The overall response rate (ORR) was 74%, with a 39% very good partial response (VGPR) rate. Median progression-free survival (PFS) and OS were 14 and 28 months, respectively. Of note, median PFS and OS were 27 months and not reached (NR), respectively, in patients who underwent stem-cell transplantation, and 2 and 12, respectively, in patients who did not ($P<0.001$ for both comparisons).

In this trial, lenalidomide for the upfront treatment of pPCL proved to be able to induce a remarkable response rate; however, in order to obtain durable remissions, initial cytoreduction must be followed by consolidation with high-dose chemotherapy and transplantation.

Pomalidomide

Pomalidomide is a third generation IMiD with a proven activity in MM[50]. So far there are very limited data on its use in PCL. The first evidence of the activity of pomalidomide, combined with dexamethasone, in a case of sPCL was reported in 2015[51].

Recently, the combination of pomalidomide, dexamethasone and pixantrone (PiPoD) was used to treat monoclonal plasma cells from two patients, both in vitro and vivo, with early signals of efficacy. [52]

Bortezomib

Case reports and retrospective analyses suggested the efficacy of bortezomib, the first in class proteasome inhibitor (PI), in both primary and secondary PCL.

In a small, retrospective cohort of 12 patients, including pPCL and sPCL, different bortezomib-based combinations were able to induce an ORR of 92%, resulting in a median PFS of 8 months and median OS of 12 months[53].

The Italian GIMEMA MM working party conducted a retrospective study on 29, previously untreated pPCL patients receiving bortezomib, combined with conventional chemotherapeutic agents, corticosteroids and thalidomide; a proportion of patients underwent subsequent stem cell transplantation (SCT). The ORR rate was 79%, with a CR rate of 28%. In 10/11 patients presenting with acute renal failure, renal function improved or reversed. At 24 months, 40% of patients were free from progression and 55% were alive. Similarly to what was reported with lenalidomide treatment, the best results were seen in patients who underwent transplantation[54].

The Greek myeloma study group retrospectively analysed 42 patients with both pPCL and sPCL between 2000 and 2013; 29 received a bortezomib-based regimen. Patients receiving bortezomib had a higher ORR (69% vs 31%) and a prolonged OS (median, 13 vs 2 months; $p<0.007$) as compared to patients who did not receive bortezomib. Of notice, among patients receiving bortezomib, median OS was 18 months in pPCL patients in comparison with 2 months in sPCL ones ($p<0.001$)[55].

The Intergoup francofone du myelome (IFM) retrospectively analysed 70 pPCL patients: transplant eligible patients were treated with conventional chemotherapy (vincristine, doxorubicin and dexamethasone, VAD) or bortezomib plus

dexamethasone (VD); transplant ineligible patients received melphalan-prednisone plus either thalidomide or bortezomib[24]. Overall, median OS was 16 months, with the best survival among transplant eligible patients (31 months, median). In this study, differently from other trials, no differences were reported among patients receiving or not bortezomib, both in transplant and non-transplant settings.

Reece et al reported a retrospective analysis of 10 newly diagnosed pPCL patients treated with CyBorD induction (median number of cycles, 4), followed by ASCT. After CyBorD induction, the ORR was 100%, with a VGPR rate of 50% and a CR rate of 20%. Stem-cell collection was successfully performed in 90% of patients. After ASCT, the CR rate increased to 44%. After a median follow-up of 25 months, median PFS was 18 months and 70% of patients were alive.[56]

The IFM conducted the first prospective phase II trial with bortezomib in first-line treatment for pPCL patients[57]. Patients up to 70 years received bortezomib, cyclophosphamide and dexamethasone (CyBorD), alternated with bortezomib, pegylated liposomial doxorubicin and dexamethasone (PAD), for 4 cycles as induction treatment. After stem-cell collection, patients received high-dose melphalan (HDM, 200 mg/m2; 140 mg/m2 in those aged 66-70 years) followed by autologous stem-cell transplantation (ASCT). After the first ASCT, patients less than 66 years of age with a donor and who achieved at least a VGPR, could proceed to allogeneic stem cell transplantation (reduced-intensity conditioning, RIC), the others underwent a second ASCT, followed by consolidation/maintenance for a year with bortezomib, lenalidomide and dexamethasone (VRD), alternated with Rd. Between 2010 and 2013, 40 patients entered the study; after induction therapy, the ORR was 69%, while 25% of patients were primary refractory. Subsequently, 65% proceeded to the first ASCT; with

HDM and ASCT, the VGPR rate increased from 26% to 38%, the CR rate increased from 10% to 38%.

After the first transplant, 41% of patients were eligible to receive allogeneic transplant, the remainders underwent a second ASCT. After a median follow-up of 29 months, median PFS and OS were 15 and 36 months, respectively. In a landmark analysis from the second transplant, patients who received a second ASCT had a longer median PFS (NR vs 11 months; p=0.04) and OS (NR vs 29 months; p=0.09) as compared to allografted patients.

The combination of a bortezomib and IMiDs, thalidomide or lenalidomide, as induction treatment has brought excellent results and is now considered a standard of care for newly diagnosed MM patients[58,59].

A recent retrospective analysis evaluated the role of VRD in sPCL patients.[60] Nine patients received a median of 3 cycles, with a 44% ORR. Overall, median PFS was 5 months, confirming the poor prognosis of sPCL, even in patients treated with an intensive regimen. Of notice, median PFS and OS were 2 months, for patients experiencing progression while on treatment, and 12 months for responders (p=0.0049).

STEM CELL TRANSPLANTATION

Data from both retrospective and prospective analyses suggest that although PCL patients may respond well to therapy, responses tend to be transient in the absence of consolidation treatment, even after induction with a novel agent. In this light, high-dose chemotherapy plus stem cell support, in transplant eligible patients, showed the best results reported among PCL patients (Table IV).

Autologous stem cell transplantation

The first evidence of the efficacy of HDM with ASCT was reported by McElwain and Powles in 1983[61]. A retrospective analysis conducted in 80 patients with PCL treated at the Mayo Clinic highlighted that patients undergoing ASCT had a significantly longer OS as compared to transplant ineligible patients (median, 34 vs 11 months)[12]. However, the survival benefit reported for ASCT patients may be at least partially explained by their younger age as compared to ASCT ineligible patients, and by the disease sensitivity to induction treatment, enabling a subsequent transplant. The largest report of ASCT in PCL comes from the European Bone Marrow Registry (EBMTR) that compared outcomes of pPCL (272 patients) and MM patients (20,844 patients) treated with ASCT[62]. In comparison with MM patients, those affected by pPCL showed higher CR rates both before transplantation (12% vs 26%) and at day +100 from ASCT (28% vs 41%). Despite a higher responsiveness of PCL to therapy, both PFS (median, 14 vs 27 months) and OS (median, 25 vs 62 months) were shorter among pPCL patients as compared to MM patients, reflecting the aggressive behaviour of PCL. The Center for International Blood & Marrow Transplant Research (CIBMTR) reported the outcomes of 97 pPLC treated with ASCT[63]. Three-year PFS and OS were 34% and 62%, respectively. Authors reported a trend toward a better OS for patients treated with tandem vs single ASCT.

Allogeneic stem cell transplantation

Given the high aggressiveness of pPCL, in the presence of a suitable donor, allogeneic stem cell transplantation has been addressed as a potentially curative approach for PCL patients.

The CIBMTR retrospectively analysed 50 pPCL patients receiving allogeneic SCT, comparing their outcomes with those of patients treated with ASCT (97 patients)[63]. A myeloablative conditioning regimen (MAC) was used in 68% of patients, while the remaining 32% received RIC. Despite a lower cumulative incidence of relapse among allografted patients as compared to autografted patients (38% vs 61%), 3-year PFS (20% vs 39%) and OS (39% vs 64%) were longer in the ASCT group. Progressive disease accounted for 22% of deaths in the allogeneic SCT group as compared to 85% in the ASCT group; on the other hand, non-relapse mortality was sensitively higher in the allo-group as compared to the ASCT group (41% vs 5%), without significant differences between patients receiving RIC or MAC.

Similar results were reported by the EBMTR that compared the outcome of 62 PCL patients treated with allo-SCT to that of 411 patients who underwent ASCT[64]. No significant differences were detected in terms of both PFS and OS between in the two groups.

In a retrospective analysis, Lebovic et al, reported better OS for patients undergoing allo-SCT who had received bortezomib as compared to those who were not treated with bortezomib (median, 28 vs 4 months)[65].

CURRENT MANAGEMENT OF PCL

Plasma cell leukemia usually presents with aggressive clinical features; hence, the first goal of treatment is to achieve fast disease control and reduce disease-related complications, thus reducing early mortality.

Transplant-eligible patients should receive induction treatment based on aggressive regimens combining chemotherapy and novel agents. Bortezomib-based

chemotherapy regimens plus IMiDs have been recommended for younger, transplant eligible patients (hyperCVAD-VTD: hyper- fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone – bortezomib, thalidomide, dexamethasone; PAD: bortezomib, doxorubicin, dexamethasone; VTD/VRD-PACE: bortezomib, thalidomide/lenalidomide, dexamethasone – cisplatin, doxorubicin, cyclophosphamide, etoposide).[11]

Bortezomib should also be preferred in the case of high proliferative rate and LDH levels or in presence of acute renal failure[47,48,57]. Lenalidomide and dexamethasone also proved to be effective, but given the slower activity, they should be preferred in patients with a less aggressive disease. Consolidation with SCT appears to prolong survival in retrospective case series[12,24]. The most promising results in terms of PFS and OS were reported with HDM and ASCT as consolidation after induction therapy, suggesting it as the best therapeutic modality currently available to achieve long-term remission[63]. Allogeneic SCT has been suggested in pPCL patients as a potentially curative approach. Despite a sensibly lower relapse rate as compared to patients undergoing ASCT, a disappointingly high non relapse mortality (NRM) rate was reported among patients who received consolidation with allogeneic SCT, thus explaining the lack of survival difference between ASCT and Allo-SCT patients[64]. Post-transplant strategies, including consolidation and/or maintenance with novel agents, should be considered to quantitatively and qualitatively improve responses and patients' outcome.

Transplant ineligible patients should receive induction treatment with a bortezomib-based combination followed by maintenance treatment. In the very elderly population and in frail patients, treatment efficacy should be carefully weighed against the risk of

life-threatening toxicities and adverse events that may significantly impair quality of life; in this respect, dose reductions could be adopted. In selected cases, a palliative approach could be offered upfront, based on patient frailty.

Unlike MM, the higher proliferative rate of plasma cells in PCL raises the risk of tumor lysis syndrome (TLS) in PCL patients, especially those presenting with impaired renal function[66]. To prevent TLS, adequate hydration is essential and either allopurinol (low-risk patients) or rasburicase (high risk patients) should be administered to prevent the renal deposition of uric acids[20].

Herpes zoster prophylaxis with acyclovir and antibacterial prophylaxis with cotrimoxazole are indicated for patients receiving bortezomib and high-dose steroids, respectively.

Thromboprophylaxis is indicated, according to individual risk, in patients treated with lenalidomide.

CONCLUSIONS AND FUTURE PERSPECTIVES

pPCL is a distinct entity from MM both from a clinical and biological point of view, as shown by several studies. Biologic markers typical of pPCL such as GEP signatures could be helpful in the future in detecting pPCL with lower (<20% and <2X10^9/L) cut-offs of plasmocytosis to avoid an under-estimation of diagnosis. Regarding sPCL, today we cannot predict the risk of developing this aggressive and often treatment-refractory pathological entity. Longitudinal tracking of large series of MM cases should be made to shed light on the clinical and molecular factors favouring secondary leukemization.

The significant improvements obtained with the introduction of new agents in MM only partially translated into an advantage also in PCL patients. The rarity of this disease and the lack of prospective trials make it difficult to generate solid data and treatment guidelines.

The availability of NA has changed, and at least partially improved, the treatment of PCL. To date, available data suggest that the response obtained with induction treatment, including NA, must be deepened with high dose chemotherapy and SCT in eligible patients. Non-transplant candidates still have a very poor outcome, only minimally increased by NA. In these patients, the aggressiveness of the disease suggests that induction with triplet followed by continuous treatment when tolerated, may be beneficial to control residual disease, but it should be evaluated in a prospective setting.

The development of newer agents with different mechanisms of actions may enrich the treatment armamentarium available against PCL; particularly, newer drugs such as the next generation PI carfilzomib and ixazomib, next generation IMIDs like pomalidomide, and monoclonal antibodies, the anti-CD38 daratumumab and isatuximab, may increase treatment efficacy. Some of these drugs have shown efficacy in high-risk MM patients, defined by FISH analysis, and therefore could be beneficial in the treatment of PCL patients, often harbouring high-risk chromosomal abnormalities such as del17. Recent data, showed the efficacy of venetoclax, (recently approved by FDA for CLL) in the treatment of MM patients harbouring t(11;14), a translocation frequently reported in pPCL, thus providing the rational for exploring the use of this drug also in patients with t(11;14) positive pPCL.

The enrolment of PCL patients in clinical trials, are essential to test complex treatment strategies and to generate evidence in this field.

Table I Diagnostic criteria of plasma cell leukemia[7]

1. >$2x10^9$/l clonal plasma cells in peripheral blood 2. >20% of blood leukocytes represented by clonal plasma cells Both criteria should be met to diagnose plasma cell leukemia (PCL)
• Primary plasma cell leukemia (pPCL): presents as *de novo* leukaemia • Secondary plasma cell leukemia (sPCL): progression from a pre-existing multiple myeloma

Table II Studies exploiting high throughput technologies in pPCL patients.

Authors	*N of pts*	*High throughput technology used*	*N of DE genes/miRNA or significant recurrently mutated genes*	*Pathways involved*
Usmani et al.[32]	13	GEP	203 genes	LXR/RXR activation, inositol metabolism, hepatic fibrosis/hepatic stellate-cell activation, LPS/IL-1 mediated inhibition of RXR function
Mosca et al.[33]	23	FISH and SNP-array integrated with GEP	NA	NA
Todoerti et al.[34]	21	GEP	503 genes	NF-kB, structural organization and migration of the cell, CD40, TGFbeta, AKT, FAS.
Lionetti et al.[35]	18	miRNA-array integrated with GEP and SNP-array	83 miRNAs	Oncogenesis, immune response, immune system, haematopoiesis
Cifola et al.[36]	12	WES integrated with GEP and SNP-array	14 significant recurrently mutated genes	Cadherin signalling, extracellular matrix-receptor interaction, Cell cycle G2/M checkpoint, Wnt signalling, extracellular matrix organization.

DE: differentially expressed; GEP: gene expression profiling; NA: not available; FISH: fluorescence in situ hybridization; SNP: single nucleotide polymorphism; WES: whole exome sequencing; miRNA: micro ribonucleic acid

Table III. Results from selected studies on NA in primary PCL patients.

Authors	*N of pts*	*Induction*	*≥PR after induction*	*Pts receiving SCT*	*PFS*	*OS*
RETROSPECTIVE STUDIES						
D'Arena et al.[54]	29	Bortezomib-based	79%	41%	40% @ 2 yr	55% @ 2 yr
Katroditou et al.[55]	25	Bortezomib-based (69%)	80%	24% (overall)	---	50% @ 18 mo
Reece et al.[56]	10	Bortezomib, Cyclophosphamide and dexamethasone	100%	90%	50% @ 18 mo	
PROSPECTIVE STUDIES						
Musto et al.[49]	23	Lenalidomide, Dexamethasone	74%	39%	50% @ 15 mo	50% @ 28 mo (median NR post-SCT)
Royer et al.[57]	40	Bortezomib, doxorubicin and dexamethasone alternating to Cyclophospha	69%	65%	50% @ 16 mo	50% @ 3 yr post-SCT

		mide, bortezomib and dexamethasone				

PFS: progression-free survival; OS: overall survival; SCT: stem cell transplant; pts: patients; mo: months; yr: year; PR: partial response; NA: not available; NR: not reached.

Table IV. Results from selected, retrospective studies with autologous and allogeneic transplantation in PCL patients.

Authors	*N of Pts*	*Preparative regimen*	*NRM*	*PFS*	*OS*
AUTOLOGOUS STEM CELL TRANSPLANT					
Drake et al.[62]	272	Various	NA	50% @ 27 mo	50% @ 25 mo
Mahindra et al.[63]	99	Various (melphalan-based 91%)	3-year: 5%	34% @ 3 yr	64% @ 3 yr
ALLOGENEIC STEM CELL TRANSPLANT					
Mahindra et al.[63]	50	MAC: 68% RIC: 32%	3-year: 41%	20% @ 3 yr	39% @ 3 yr
Morris et al.[64]	62	MAC: 73% RIC: 27%	NA	MAC: 19% @ 5 yr RIC: 11% @ 5 yr	MAC: 27% @ 5 yr RIC: 19% @ 5 yr

PFS: progression-free survival; OS: overall survival; pts: patients; mo: months; yr: year; NA: not available; STC: stem cell transplant; NRM: non-relapse mortality; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning.

References:

1. Ramsingh G, Mehan P, Luo J, Vij R, Morgensztern D. Primary plasma cell leukemia: a Surveillance, Epidemiology, and End Results database analysis between 1973 and 2004. *Cancer*. 2009;115(24):5734-5739. doi:10.1002/cncr.24700.
2. Dimopoulos MA, Palumbo A, Delasalle KB, Alexanian R. Primary plasma cell leukaemia. *Br J Haematol*. 1994;88(4):754-759. http://www.ncbi.nlm.nih.gov/pubmed/7819100. Accessed July 13, 2016.
3. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010;116(19):3724-3734. doi:10.1182/blood-2010-05-282632.
4. Kyle RA, Maldonado JE, Bayrd ED. Plasma cell leukemia. Report on 17 cases. *Arch Intern Med*. 1974;133(5):813-818.
5. Mohite S, Baladandayuthapani V, Thomas SK, et al. Circulating Plasma Cells By Routine Complete Blood Count Identify Patients With Similar Outcome As Plasma Cell Leukemia. Shah RA, ed. *Blood*. 2013;122(21):5356.
6. An G, Qin X, Acharya C, et al. Multiple myeloma patients with low proportion of circulating plasma cells had similar survival with primary plasma cell leukemia patients. *Ann Hematol*. 2015;94(2):257-264. doi:10.1007/s00277-014-2211-0.
7. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757. http://www.ncbi.nlm.nih.gov/pubmed/12780789. Accessed July 13, 2016.
8. Musto P, Simeon V, Todoerti K, Neri A. Primary Plasma Cell Leukemia: Identity

Card 2016. *Curr Treat Options Oncol*. 2016;17(4):19. doi:10.1007/s11864-016-0392-6.

9. Jelinek T, Kryukov F, Rihova L, Hajek R. Plasma cell leukemia: from biology to treatment. *Eur J Haematol*. 2015;95(1):16-26. doi:10.1111/ejh.12533.
10. Albarracin F, Fonseca R. Plasma cell leukemia. *Blood Rev*. 2011;25(3):107-112. doi:10.1016/j.blre.2011.01.005.
11. Fernández de Larrea C, Kyle RA, Durie BGM, et al. Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. *Leukemia*. 2013;27(4):780-791. doi:10.1038/leu.2012.336.
12. Tiedemann RE, Gonzalez-Paz N, Kyle RA, et al. Genetic aberrations and survival in plasma cell leukemia. *Leukemia*. 2008;22(5):1044-1052. doi:10.1038/leu.2008.4.
13. García-Sanz R, Orfão A, González M, et al. Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. *Blood*. 1999;93(3):1032-1037. http://www.ncbi.nlm.nih.gov/pubmed/9920853. Accessed July 13, 2016.
14. Bladé J, Kyle RA. Nonsecretory myeloma, immunoglobulin D myeloma, and plasma cell leukemia. *Hematol Oncol Clin North Am*. 1999;13(6):1259-1272.
15. Noel P, Kyle RA. Plasma cell leukemia: an evaluation of response to therapy. *Am J Med*. 1987;83(6):1062-1068.
16. Gonsalves WI, Rajkumar SV, Go RS, et al. Trends in survival of patients with primary plasma cell leukemia: a population-based analysis. *Blood*. 2014;124(6):907-912. doi:10.1182/blood-2014-03-565051.

17. Mangiacavalli S, Pochintesta L, Cocito F, et al. Correlation between burden of 17P13.1 alteration and rapid escape to plasma cell leukaemia in multiple myeloma. *Br J Haematol*. 2013;162(4):555-558. doi:10.1111/bjh.12385.

18. Kraj M, Kopeć-Szlęzak J, Pogłód R, Kruk B. Flow cytometric immunophenotypic characteristics of 36 cases of plasma cell leukemia. *Leuk Res*. 2011;35(2):169-176. doi:10.1016/j.leukres.2010.04.021.

19. Vande Broek I, Van de Broek I, Leleu X, et al. Clinical significance of chemokine receptor (CCR1, CCR2 and CXCR4) expression in human myeloma cells: the association with disease activity and survival. *Haematologica*. 2006;91(2):200-206.

20. van de Donk NWCJ, Lokhorst HM, Anderson KC, Richardson PG. How I treat plasma cell leukemia. *Blood*. 2012;120(12):2376-2389. doi:10.1182/blood-2012-05-408682.

21. Pellat-Deceunynck C, Barillé S, Jego G, et al. The absence of CD56 (NCAM) on malignant plasma cells is a hallmark of plasma cell leukemia and of a special subset of multiple myeloma. *Leukemia*. 1998;12(12):1977-1982.

22. Guo J, Su J, He Q, et al. The prognostic impact of multiparameter flow cytometry immunophenotyping and cytogenetic aberrancies in patients with multiple myeloma. *Hematology*. February 2016:1-10. doi:10.1179/1607845415Y.0000000010.

23. Murray ME, Gavile CM, Nair JR, et al. CD28-mediated pro-survival signaling induces chemotherapeutic resistance in multiple myeloma. *Blood*. 2014;123(24):3770-3779. doi:10.1182/blood-2013-10-530964.

24. Avet-Loiseau H, Roussel M, Campion L, et al. Cytogenetic and therapeutic

characterization of primary plasma cell leukemia: the IFM experience. *Leukemia*. 2012;26(1):158-159. doi:10.1038/leu.2011.176.

25. Avet-Loiseau H, Daviet A, Brigaudeau C, et al. Cytogenetic, interphase, and multicolor fluorescence in situ hybridization analyses in primary plasma cell leukemia: a study of 40 patients at diagnosis, on behalf of the Intergroupe Francophone du Myélome and the Groupe Français de Cytogénétique Hématolo. *Blood*. 2001;97(3):822-825.

26. Chiecchio L, Dagrada GP, White HE, et al. Frequent upregulation of MYC in plasma cell leukemia. *Genes Chromosomes Cancer*. 2009;48(7):624-636. doi:10.1002/gcc.20670.

27. Chang H, Qi X, Yeung J, Reece D, Xu W, Patterson B. Genetic aberrations including chromosome 1 abnormalities and clinical features of plasma cell leukemia. *Leuk Res*. 2009;33(2):259-262. doi:10.1016/j.leukres.2008.06.027.

28. Chng WJ, Price-Troska T, Gonzalez-Paz N, et al. Clinical significance of TP53 mutation in myeloma. *Leukemia*. 2007;21(3):582-584. doi:10.1038/sj.leu.2404524.

29. Eymin B, Gazzeri S, Brambilla C, Brambilla E. Mdm2 overexpression and p14(ARF) inactivation are two mutually exclusive events in primary human lung tumors. *Oncogene*. 2002;21(17):2750-2761. doi:10.1038/sj.onc.1205359.

30. Stott FJ, Bates S, James MC, et al. The alternative product from the human CDKN2A locus, p14(ARF), participates in a regulatory feedback loop with p53 and MDM2. *EMBO J*. 1998;17(17):5001-5014. doi:10.1093/emboj/17.17.5001.

31. Simeon V, Todoerti K, La Rocca F, et al. Molecular Classification and Pharmacogenetics of Primary Plasma Cell Leukemia: An Initial Approach toward

Precision Medicine. *Int J Mol Sci*. 2015;16(8):17514-17534. doi:10.3390/ijms160817514.

32. Usmani SZ, Nair B, Qu P, et al. Primary plasma cell leukemia: clinical and laboratory presentation, gene-expression profiling and clinical outcome with Total Therapy protocols. *Leukemia*. 2012;26(11):2398-2405. doi:10.1038/leu.2012.107.

33. Mosca L, Musto P, Todoerti K, et al. Genome-wide analysis of primary plasma cell leukemia identifies recurrent imbalances associated with changes in transcriptional profiles. *Am J Hematol*. 2013;88(1):16-23. doi:10.1002/ajh.23339.

34. Todoerti K, Agnelli L, Fabris S, et al. Transcriptional characterization of a prospective series of primary plasma cell leukemia revealed signatures associated with tumor progression and poorer outcome. *Clin Cancer Res*. 2013;19(12):3247-3258. doi:10.1158/1078-0432.CCR-12-3461.

35. Lionetti M, Musto P, Di Martino MT, et al. Biological and clinical relevance of miRNA expression signatures in primary plasma cell leukemia. *Clin Cancer Res*. 2013;19(12):3130-3142. doi:10.1158/1078-0432.CCR-12-2043.

36. Cifola I, Lionetti M, Pinatel E, et al. Whole-exome sequencing of primary plasma cell leukemia discloses heterogeneous mutational patterns. *Oncotarget*. 2015;6(19):17543-17558. doi:10.18632/oncotarget.4028.

37. Egan JB, Shi C-X, Tembe W, et al. Whole-genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution, and clonal tides. *Blood*. 2012;120(5):1060-1066. doi:10.1182/blood-2012-01-405977.

38. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012;120(5):1067-1076. doi:10.1182/blood-2012-01-405985.

39. Costello R, Sainty D, Bouabdallah R, Fermand JP, Delmer A, Diviné M, Marolleau JP, Gastaut JA, Olive D, Rousselot P CP. Primary plasma cell leukaemia: a report of 18 cases. *Leuk Res*. 2001;25(2):103-107.

40. Bernasconi C, Castelli G, Pagnucco G, Brusamolino E. Plasma cell leukemia: a report on 15 patients. *Eur J Haematol Suppl*. 1989;51:76-83. http://www.ncbi.nlm.nih.gov/pubmed/2697596. Accessed July 13, 2016.

41. Jiménez-Zepeda VH, Domínguez VJ. Plasma cell leukemia: a rare condition. *Ann Hematol*. 2006;85(4):263-267. doi:10.1007/s00277-005-0054-4.

42. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520. doi:10.1182/blood-2007-10-116129.

43. Petrucci MT, Martini V, Levi A, et al. Thalidomide does not modify the prognosis of plasma cell leukemia patients: experience of a single center. *Leuk Lymphoma*. 2007;48(1):180-182. doi:10.1080/10428190601007570.

44. Johnston RE, Abdalla SH. Thalidomide in low doses is effective for the treatment of resistant or relapsed multiple myeloma and for plasma cell leukaemia. *Leuk Lymphoma*. 2002;43(2):351-354. doi:10.1080/10428190290006143.

45. Bauduer F. Efficacy of thalidomide in the treatment of VAD-refractory plasma cell leukaemia appearing after autologous stem cell transplantation for multiple myeloma. *Br J Haematol*. 2002;117(4):996-997. http://www.ncbi.nlm.nih.gov/pubmed/12060146. Accessed July 13, 2016.

46. Benson DM, Smith MK. Effectiveness of lenalidomide (Revlimid) for the treatment of plasma cell leukemia. *Leuk Lymphoma*. 2007;48(7):1423-1425. doi:10.1080/10428190701361851.

47. Musto P, Pietrantuono G, Guariglia R, Villani O, Martorelli MC, D'Auria F, Zonno A LR. Salvage therapy with lenalidomide and dexamethasone in relapsed primary plasma cell leukemia. 2008;32(10):1637-1638.

48. Guglielmelli T, Merlini R, Giugliano E, Saglio G. Lenalidomide, melphalan, and prednisone association is an effective salvage therapy in relapsed plasma cell leukaemia. *J Oncol*. 2009;2009:867380. doi:10.1155/2009/867380.

49. Musto P, Simeon V, Martorelli MC, et al. Lenalidomide and low-dose dexamethasone for newly diagnosed primary plasma cell leukemia. *Leukemia*. 2014;28(1):222-225. doi:10.1038/leu.2013.241.

50. Gay F, Mina R, Troia R, Bringhen S. Pharmacokinetic evaluation of pomalidomide for the treatment of myeloma. *Expert Opin Drug Metab Toxicol*. 2013;9(11):1517-1527. doi:10.1517/17425255.2013.827169.

51. Mele G, Coppi MR, Guaragna G, Spina A MA. Response to pomalidomide plus fixed low-dose dexamethasone in a case of secondary plasma cell leukaemia. *Leuk Res*. 2016. doi:10.1016/j.leukres.2015.11.009.

52. Willenbacher E, Willenbacher W, Gastl G, Verdorfer I, Kircher B. In-Vitro Actvity of Pixantrone (PIX) in Plasma Cell Leukaemia (PCL) and Early Clinical Activity in a Pixantrone–Pomalidomide–Dexamethasone (PiPoD) Combination. *Blood*. 2014;124(21):5732-5732.

53. Musto P, Rossini F, Gay F, et al. Efficacy and safety of bortezomib in patients with plasma cell leukemia. *Cancer*. 2007;109(11):2285-2290.

doi:10.1002/cncr.22700.

54. D'Arena G, Valentini CG, Pietrantuono G, et al. Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: a retrospective study from GIMEMA Multiple Myeloma Working Party. *Ann Oncol*. 2012;23(6):1499-1502. doi:10.1093/annonc/mdr480.

55. Katodritou E, Terpos E, Kelaidi C, Kotsopoulou M, Delimpasi S, Kyrtsonis MC, Symeonidis A, Giannakoulas N, Stefanoudaki A, Christoulas D, Chatziaggelidou C, Gastari V, Spyridis N, Verrou E, Konstantinidou P, Zervas K DM. Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: Analysis of the Greek myeloma study group. *Am J Hematol*. 2014;89(2):145-150.

56. Reece DE, Phillips M, Chen CI, et al. Induction Therapy With Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) For Primary Plasma Cell Leukemia (pPCL). *Blood*. 2013;122(21).

57. Royer B, Minvielle S, Diouf M, et al. Bortezomib, Doxorubicin, Cyclophosphamide, Dexamethasone Induction Followed by Stem Cell Transplantation for Primary Plasma Cell Leukemia: A Prospective Phase II Study of the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2016;34(18):2125-2132. doi:10.1200/JCO.2015.63.1929.

58. Cavo M, Pantani L, Pezzi A, et al. Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. *Leukemia*. 2015;29(12):2429-2431. doi:10.1038/leu.2015.274.

59. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010;116(5):679-686. doi:10.1182/blood-2010-02-268862.

60. Jimenez-Zepeda VH, Reece DE, Trudel S, Chen C, Tiedemann R, Kukreti V. Lenalidomide (Revlimid), bortezomib (Velcade) and dexamethasone for the treatment of secondary plasma cell leukemia. *Leuk Lymphoma*. 2015;56(1):232-235. doi:10.3109/10428194.2014.893304.

61. McElwain TJ PR. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. *Lancet*. 1983;2(8354):822-824.

62. Drake MB, Iacobelli S, van Biezen A, et al. Primary plasma cell leukemia and autologous stem cell transplantation. *Haematologica*. 2010;95(5):804-809. doi:10.3324/haematol.2009.013334.

63. Mahindra A, Kalaycio ME, Vela-Ojeda J, et al. Hematopoietic cell transplantation for primary plasma cell leukemia: results from the Center for International Blood and Marrow Transplant Research. *Leukemia*. 2012;26(5):1091-1097. doi:10.1038/leu.2011.312.

64. Morris C, Iacobelli S, Gahrton G, Garderet L, Drake M, van Biezen A, Mohty M, Blaise D, Poire X, Kersten M J, Milpied N-J, Lenhoff S, Russell NH, Finke J de WT. Has Allogeneic Transplantation a Role in the Management of Plasma Cell Leukaemia? A Study on Behalf of the Myeloma Subcomittee of the Chronic Leukaemia Working Party of the EBMT. *Blood*. 2011;118(21):abstr 877.

65. Lebovic D, Zhang L, Alsina M, Nishihori T, Shain KH, Sullivan D, Ochoa-Bayona JL, Kharfan-Dabaja MA BR. Clinical outcomes of patients with plasma cell leukemia in the era of novel therapies and hematopoietic stem cell transplantation

strategies: a single-institution experience. 2011;11(6):507-511.

66. Jaskiewicz AD, Herrington JD, Wong L. Tumor lysis syndrome after bortezomib therapy for plasma cell leukemia. *Pharmacotherapy*. 2005;25(12):1820-1825. doi:10.1592/phco.2005.25.12.1820.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
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Corresponding Author's Name: Roberto Mina

5. Manuscript Title: Plasma cell leukemia: update on biology and therapy

6. Manuscript Identifying Number (if you know it): GLAL-2016-0755

Section 2. The Work Under Consideration for Publication

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Dr. D'Agostino has nothing to disclose.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

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Section 1. Identifying Information

1. Given Name (First Name): Chiara
2. Surname (Last Name): Cerrato
3. Date: 26-July-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Roberto Mina

5. Manuscript Title: Plasma cell leukemia: update on biology and therapy

6. Manuscript Identifying Number (if you know it): GLAL-2016-0755

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Francesca
2. Surname (Last Name): Gay
3. Date: 26-July-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Roberto Mina

5. Manuscript Title: Plasma cell leukemia: update on biology and therapy

6. Manuscript Identifying Number (if you know it): GLAL-2016-0755

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☐	☑	☐	☐	Honoraria
BMS	☐	☑	☐	☐	Honoraria
Celgene	☐	☑	☐	☐	Honoraria
Takeda	☐	☑	☐	☐	Honoraria; Advisory Committee
Janssen	☐	☑	☐	☐	Advisory Committee
Mundipharma	☐	☑	☐	☐	Advisory Committee

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Section 4. Intellectual Property -- Patents & Copyrights

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Dr. Gay reports personal fees from Amgen, personal fees from BMS, personal fees from Celgene, personal fees from Takeda, personal fees from Janssen, personal fees from Mundipharma, outside the submitted work; .

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Section 1. Identifying Information

1. Given Name (First Name): Antonio
2. Surname (Last Name): Palumbo
3. Date: 26-July-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Roberto Mina

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Amgen	☐	☑	☐	☐	Honoraria; Consultancy; Research support
Novartis	☐	☑	☐	☐	Honoraria; Consultancy; Research support
BMS	☐	☑	☐	☐	Honoraria; Consultancy; Research support
Genmab	☐	☑	☐	☐	Honoraria; Consultancy; Research support
Celgene	☐	☑	☐	☐	Honoraria; Consultancy; Research support

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Janssen	☐	☑	☐	☐	Honoraria; Consultancy; Research support
Takeda	☐	☑	☐	☐	Employee; Honoraria; Consultancy; Research support
Sanofi	☐	☑	☐	☐	Honoraria; Consultancy; Research support
Merck	☐	☑	☐	☐	Honoraria; Consultancy; Research support
Binding Site	☐	☑	☐	☐	Research support

Section 4. Intellectual Property -- Patents & Copyrights

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