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Primary Plasma Cell Leukemia displaying t(11;14) have specific genomic, transcriptional and clinical feature.

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KEY POINTS

Key point#1:

Primary PCL displays specific genomic and transcriptomic profile when compared to newly diagnosed myeloma.

Key point #2:

Primary PCL with t(11;14) is a distinct genomic and transcriptional entity, with better overall survival.

ABSTRACT

Primary plasma cell leukemia (pPCL) is an aggressive form of multiple myeloma (MM) that has not benefited from recent therapeutic advances in the field. Because very rare and heterogeneous, it remains poorly understood at the molecular level. To address this issue, we performed DNA and RNA sequencing of sorted plasma cells from a large cohort of 90 newly diagnosed pPCL, and compared to MM. We observed that pPCL presents a specific genomic landscape with a high prevalence of t(11;14) (about half) and high-risk genomic features such as del(17p), gain 1q, del(1p32). In addition, pPCL displays a specific transcriptome when compared to MM. We then aimed at specifically characterize pPCL with t(11;14). We observed that this sub-entity displayed significantly fewer adverse cytogenetic abnormalities. This translated into better overall survival when compared to pPCL without t(11;14) (39.2 months vs 17.9 months, $p=0.002$). Finally, pPCL with t(11;14) displayed a specific transcriptome, including differential expression of *BCL2* family members. This study is the largest series of patients with pPCL reported so far.

INTRODUCTION

Plasma cell leukemia (PCL) is a rare and aggressive form of multiple myeloma (MM), defined by the presence of more than 20% of plasma cells in the peripheral blood and/or a plasma cell count greater than $2.10^9/L$.¹ It represents 2 to 4% of multiple myeloma cases, i.e., 0.04 cases per 100,000 people per year.² It is said to be primary (pPCL) if it occurs "*de novo*" or secondary (sPCL) if it corresponds to a leukemic transformation of a previously known myeloma. pPCL accounts for 60-70% of PCL.

Compared to MM, pPCL displays distinct biological and clinical features,^{3,4} such as a younger age at diagnosis, a more aggressive presentation with frequent extramedullary diseases, and fewer lytic bone lesions. Despite the improvement of MM therapy, pPCL continues to have a poor prognosis with a median overall survival between 18 and 36 months.⁵⁻⁸

Given the low incidence and the heterogeneity of pPCL, biological knowledge is lacking, especially the molecular process responsible for its aggressiveness. To address this issue, we took advantage of a large series of pPCL to describe the genomic and transcriptomic landscape of pPCL. Given the high incidence of t(11;14) that we and others^{9,10} observed in this disease, we aimed to determine if this subgroup displayed a specific genomic profile and a better clinical outcome.

METHODS

Between 2014 and 2020, bone marrow samples were collected from 90 newly diagnosed pPCL patients within hospitals involved in the Intergroupe Francophone du Myélome (IFM) and shipped overnight to Toulouse central laboratory. All patients provided informed consent. This study was approved by the Toulouse Ethics Committee. Plasma cells were sorted from bone marrow samples using CD138 immunomagnetic cell sorting (>90% purity). DNA and RNA sequencing were performed using NextSeq 500 (Illumina). Data obtained from pPCL samples were compared to those from 907 and 288 newly diagnosed MM, respectively. Technical details of sequencing and bioinformatics analysis are available in supplementary method.

To evaluate overall survival of pPCL patients according to t(11;14) status, we selected 128 patients for whom clinical data were available, diagnosed between 2000 and 2020, followed up for > 18 months or having died from pPCL, and for whom t(11;14) was established by NGS (53 patients out of 90 from sequencing cohort) or by FISH as previously described (75 additional patients) (see supplemental Figure 1). Clinical data and treatment regimens of these 128 patients are presented in supplementary Table 1. Survival rate was estimated by the Kaplan-Meier method. Tests were two-sided and p-values <0.05 were considered significant. Statistical analysis was conducted using R®.

Data Sharing

Data for this manuscript can be found under accession number PRJNA804686.

RESULTS AND DISCUSSION

Genome analysis on 90 patients highlighted a specific genomic profile of pPCL (**Figure 1A**). Among the cytogenetic abnormalities, pPCL patients displayed higher incidences of t(11;14) (51.1% vs 23.1%, $p < 0.001$) and t(14;16) (14.4% vs 3.4%, $p < 0.001$), but an identical incidence of t(4;14) (11.1% vs 9.8%, $p = 0.7$). Hyperdiploidy was less frequent in pPCL compared with MM (20.0% vs 56.9%, $p < 0.0001$), with less trisomy 5 (7.8% vs 44.4%, $p < 0.0001$). We observed that pPCL presented higher incidence of adverse secondary lesions compared to MM, such as deletion 17p (30.0% vs 9.5%, $p < 0.0001$); including 12.2% vs 3.1% of *TP53* bi allelic inactivation, $p < 0.0001$) and gain 1q (53.3% vs 31.9%, $p < 0.001$; including 11.1% vs 5.3% of amplification 1q, $p < 0.05$), but also deletion 1p32 (24.4% vs 9.4%, $p < 0.001$). Our results are consistent with previous reports on smaller series.^{9,11-16} Despite their heterogeneity, pPCL present a specific genomic landscape with a high prevalence of t(11;14) (about half) and high-risk genomic features.

RNA seq analysis also highlighted the specificity of pPCL. Indeed, unsupervised hierarchical clustering analysis showed two distinctive cluster groups between pPCL (n=80) and MM (n=288) (**Figure 1B**). We found 2835 genes upregulated and 4070 downregulated in pPCL. Amongst top upregulated genes, we observed *FAM72D*, recently identified as a 1q21 marker of proliferation,¹⁷ and *TOX2*, that belongs to the 15-genes prognostic classifier described by the IFM¹⁸ (**Figure 1C**). Interestingly, we also observed a downregulation of the inhibitor of osteoblastic differentiation *DKK1* and the osteoclast activating factor M-CSF. GSEA analyses revealed an upregulation of genes involved in the cell cycle, fatty acid metabolism and spliceosome, and a downregulation of genes involved in adhesion, extracellular matrix, *KRAS* signaling, and B12 vitamin metabolism (**Figure 1D**). These biological differences may explain the distinct clinical features such as more proliferating presentation and more diffusion to extramedullary sites in pPCL, but fewer bone lytic lesions. Although the small size of previous pPCL cohorts, upregulation of genes involved in the spliceosome was also recently described,¹⁰ and downregulation of adhesion molecules and extracellular matrix proteins too.¹⁵

Given the large frequency of t(11;14) in pPCL, we aimed at specifically characterizing this subgroup. Interestingly, pPCL with t(11;14) tended to display more *TP53* mutations (34.0% vs 16.0%, $p = 0.054$), but this was associated to a deletion 17p only in half cases, whereas all *TP53* mutations for the non t(11;14) subgroup were bi-allelic inactivation. Importantly, pPCL with t(11;14) had fewer adverse cytogenetic abnormalities such as gain 1q (29.7% vs 79.1%, $p < 0.0005$), including amplification 1q

(2.1% vs 20.9%, $p < 0.01$), and deletion 1p32 (8.5% vs 41.9%, $p < 0.001$) (**Figure 2A**). Only 10% of the pPCL with t(11;14) had at least 2 lesions among deletion 17p, gain 1q and deletion 1p32, whereas it was 46% for the non t(11;14) subgroup ($p < 0.0005$). In addition, t(4;14) and t(14;16) pPCL were by definition exclusively present in the non t(11;14) subgroup. As expected, all these differences translated into a better outcome since median overall survival for pPCL patients with t(11;14) was significantly longer than those without t(11;14) (39.2 months vs 17.9 months, respectively, $p = 0.002$) (**Figure 2B**). Gene expression profile showed that pPCL with and without t(11;14) clustered in two distinct groups (**Figure 2C**). We found 875 genes upregulated and 1214 downregulated in pPCL with t(11;14). As expected, among the most upregulated genes was CCND1. As recently shown by Todoerti et al,¹⁹ several members of the BCL2 family genes were also significantly differentially expressed between pPCL subgroups. We observed that *PMAIP1* and *BCL2L15* were overexpressed, and *BCL2L1* and *BAK1* underexpressed. Although a fold change < 2 , *BCL-2* and *BCL2-L2* were also overexpressed and *BAX* underexpressed, when compared to non t(11;14) subgroup. Furthermore, as recently shown in MM with t(11;14),^{19,20} pPCL with t(11;14) displayed an upregulation of immature B cell markers *PAX5* and *CD79A* (**Figure 2D**), supporting the BCL2 dependency and suggesting a distinctive oncogenic mechanism for this subgroup. GSEA analyses also revealed a downregulation of genes involved in the cell cycle, NRAS and KRAS pathways, adhesion and extracellular matrix (**Figure 2E**). Of note, although a small cluster of pPCL with t(11;14) was present in the same branch as the non t(11;14) subgroup, BCL2 members family and CCND1 expression and outcome were similar as the larger cluster of pPCL with t(11;14). Globally, we highlighted that pPCL with t(11;14) is a distinguishable entity, which may notably be less proliferative, in accordance to a better prognosis, but probably more BCL2 dependent. Venetoclax, a BCL2 inhibitor, had evidence of efficacy in t(11;14) MM.^{21,22} Our results are consistent with the efficacy of Venetoclax also described in PCL patients,^{23,24} and support its evaluation in clinical trials, especially for patients with t(11;14).

In summary, we performed a study on the largest series of patients with pPCL reported so far. Using high throughput technologies, we demonstrated that pPCL had a specific genomic and transcriptomic landscape that may explain its biological and clinical features. It would be useful to extend this analysis to pPCL defined from 5% of circulating plasma cells.²⁵ We also described the biological and clinical specificities of t(11;14) pPCL, supporting the use of novel therapeutic approaches such as BCL2 inhibitors but prospective studies are necessary to confirm it.

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AUTHORSHIP CONTRIBUTION

J.C. and H.A-L. designed the research and analyzed data; TC, L.B., S.M., A.S., performed the analysis; L.D., R.L., L.P. performed the bioinformatics analysis ; TC, J.C. and H.A-L. wrote the manuscript, which was reviewed and edited by the other coauthors; All other authors provided study samples and clinical data.

DISCLOSURE OF CONFLICT-OF-INTEREST

The authors declare no competing financial interests.

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FIGURE LEGEND

Figure 1: Genomic and transcriptome of malignant plasma cells from primary PCL compared to newly diagnosed multiple myeloma. (A) Incidence of main cytogenetics abnormalities and mutations in 90 primary PCL compared to 907 newly diagnosed MM, ***p<0.0001, **p<0.005. (B) Unsupervised clustering of 90 primary PCL and 288 newly diagnosed MM based on the expression levels of the 100

most variable genes. (C) Gene expression profiling comparing differentially expressed genes between primary PCL and newly diagnosed MM, with at least twofold change ($p < 0.05$, $FDR < 0.01$). (D) GSEA analysis from 90 primary PCL compared to 288 newly diagnosed MM.

Figure 2. Genomic and transcriptome of malignant plasma cells from primary PCL displaying t(11;14) compared to primary PCL without t(11;14). (A) Incidence of main cytogenetics abnormalities and mutations in 46 primary PCL displaying t(11;14) compared to 44 primary PCL without t(11;14), $**p < 0.0001$, $*p < 0.01$. (B) Kaplan-Meier overall survival of primary PCL patients according to t(11;14). (C) Unsupervised clustering of 46 primary PCL displaying t(11;14) and 44 primary PCL without t(11;14) based on the expression levels of the 100 most variable genes. (D) Gene expression profiling comparing differentially expressed genes between primary PCL displaying t(11;14) and primary PCL without t(11;14), with at least twofold change ($p < 0.05$, $FDR < 0.01$). (E) GSEA analysis from 46 primary PCL displaying t(11;14) and 44 primary PCL without t(11;14).

Figure 1

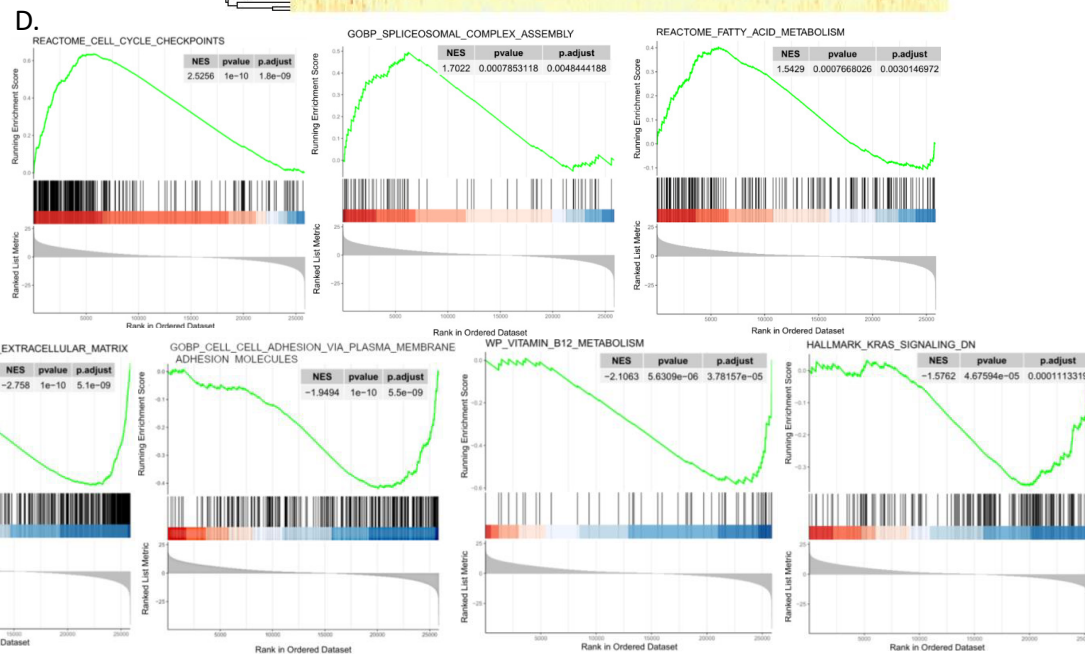
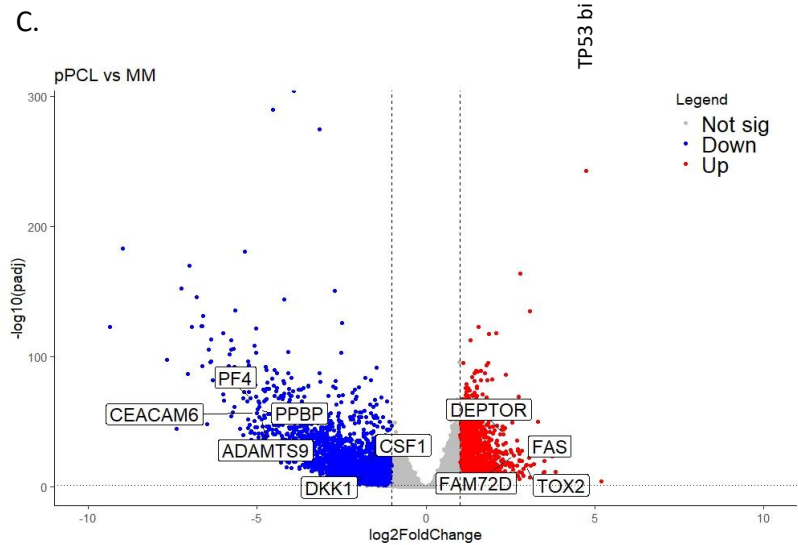
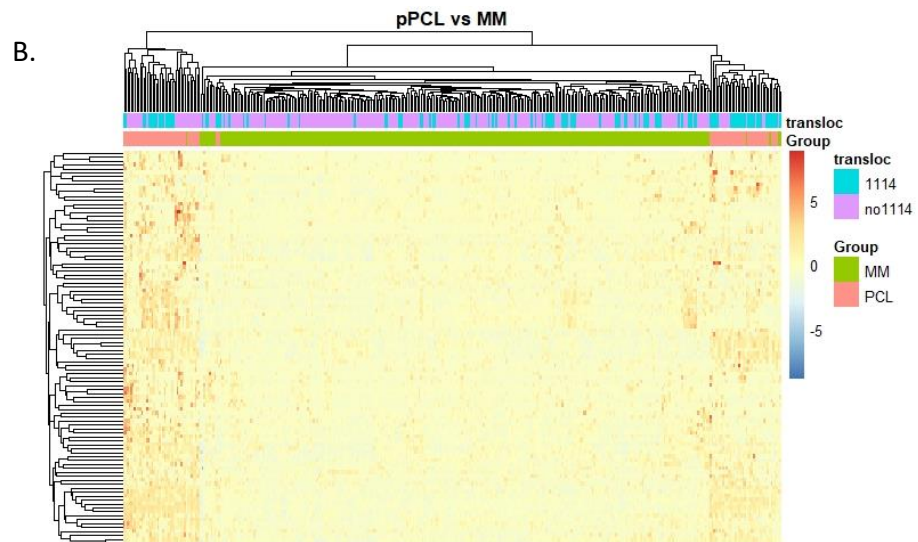
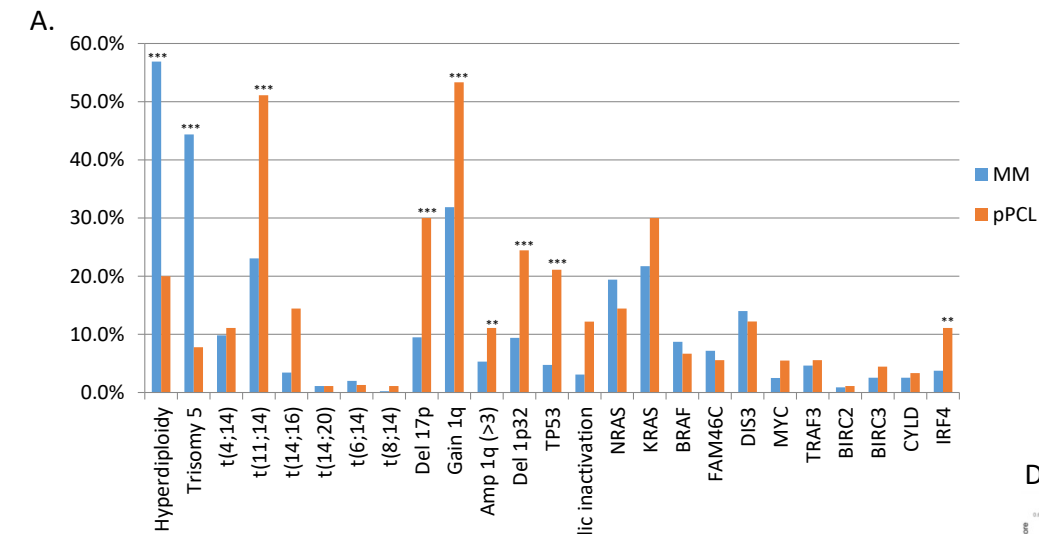


Figure 2

