Abstract: P821

Title: CLINICAL HETEROGENEITY AND OUTCOME OF PURE RED CELL APLASIA (PRCA): A MULTICENTER INTERNATIONAL STUDY

Abstract Type: Poster Presentation

Topic: Bone marrow failure syndromes incl. PNH - Clinical

Background:

PRCA is characterized by severe reticulocytopenic anemia and significant depletion of bone marrow erythroid precursors (BM). Acquired PRCA can be idiopathic or associated with autoimmune diseases, thymoma, or lymphoproliferative disorders. A transient form of PRCA is caused by parvovirus B19 (PVB19) infection. Due to the rarity of the condition and the absence of clinical-trials, guidelines on the management of PRCA are lacking.

Aims:

To evaluate clinical features, treatment and outcomes of adult PRCA patients.

Methods:

In this international multicenter study, adult PRCA patients from 13 Centers across Europe were included. PRCA was defined as normocytic normochromic anemia with severe reticulocytopenia and reduction (<5%) / absence of BM erythroid precursors. Congenital forms were excluded. Clinical and laboratory features at diagnosis, therapy lines and responses were retrospectively collected. Complete response was defined as Hb > 12g/dL, and partial as achievement of transfusion independence.

Results:

As shown in Table 1, 43 patients followed for a median of 37 months (range 1-209) were included. Median age was 62 years (29-93), with a slight female predominance; 60 % of patients had a secondary PRCA, due to autoimmune diseases (23%), thymoma (21%), or lymphoproliferative disorders (14%, 3 chronic lymphocytic leukemia, 2 T-cell large granular lymphocytic leukemia, 1 follicular lymphoma), and one associated PVB19 infection. BM evaluation showed erythroid aplasia and, in 51% of patients, a lymphoid infiltrate (median of infiltration 19%, 6-91) with a predominant T-cell phenotype in 54% of cases. Karyotype analysis was normal in all but one with chromosome Y deletion. Blood counts at diagnosis were consistent with severe reticulocytopenic anemia (median Hb 5.7, 3.5-9.6), whilst other lineages were not affected. Serum erythropoietin was increased in most subjects, and 4 had positive direct antiglobulin test, without signs of hemolysis. Median number of therapies was 3 (0-6); 81% of patients underwent steroid therapy, with 59% overall response (Table 1). Cyclosporine (CsA), used in 72% of patients, induced a response in 75%, complete in 59%; 13% of patients experienced dose reduction or withdrawal due to toxicity. Eight out of 9 patients with concomitant thymoma underwent thymectomy and 2 received thymus irradiation, without response. Further lines included mTOR inhibitors (sirolimus, everolimus) in 6 patients (66% responses); anti-CD20 monoclonal antibodies in 10, cyclophosphamide in 10, erythropoietin in 6, anti-thymocyte globulin, and anti-IL6 in 1 each. One patient died after an ineffective allogeneic transplantation. PVB19-associated PRCAs recovered spontaneously. NGS analysis, available in 11 patients (23%), showed a single somatic mutation in 4 (DNMT3A, TP53, ASXL1, TET2), and multiple mutations in 1 (EZH2, U2AF, NRAS, ASXL1, KRAS, TP53). No clear predictors of response to immunosuppressive therapy emerged except for a higher T-cell lymphoid infiltrate in the BM of subjects responding to cyclosporine. At last follow up, 21% of patients had died, mostly due to infection (67%). Mortality was associated with a diagnosis of secondary PRCA (94 vs 69%, p=0.05).

Summary/Conclusion:

Our data suggest that PRCA usually presents in elderly patients with very severe transfusion-dependent anemia

and an associated condition in 2/3 of cases. Immunosuppression, mainly with cyclosporine, is effective in >70% of patients; however, toxicity and underlying disease are associated with a non-negligible mortality rate. The utility of NGS analysis in PCRA patients will require further investigation.

Follow-up, months	37 (1-209)
Age, years	62 (29-93)
Sex, N (%)	Male 18 (42) Female 25 (58)
Associated condition, N (%)	27 (63)
Specifics of associated condition, N (%)	Autoimmune disease: 10 (23) Thymoma: 9 (21) CLL: 3 (7) T-LGL leukemia: 2 (5) Follicular lymphoma: 1 (2) MDS: 1 (2) Parvovirus B19: 1 (2)
BM lymphocyte infiltration, N (%)	22 (51)
% BM lymphocyte infiltration	19 (6-91)
Hb, g/dL	5,7 (3,5-9,6)
Reticulocyte count, x10^{9}/L	6 (0,6 – 300)
EPO, U/L	876 (29-3000)
Number of therapies	3 (0-6)
Steroid therapy, N (%)	35 (81)
Response, N (%)	CR 13 (37) PR 8 (22) NR 14 (41)
CsA therapy, N (%)	31 (72)
Response, N (%)	CR 17 (54) PR 6 (19) NR 8 (25)
Thymectomy, N (%)	8 (19)
Response, N (%)	PR 2 (25) NR 6 (75)
Other therapies, N (%)	Erythropoietin 6 (14) Cyclophosphamide 10 (23) Rituximab 10 (23) mTOR inhibitor 5 (12) Thymus irradiation 2 (5)
Alive, N (%)	34 (79)

Keywords: Anemia, Bone marrow failure, Cyclosporin A, Pure red cell aplasia