Aplastic anemia in the elderly: a nationwide survey on behalf of the French Reference Center for Aplastic Anemia

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ABSTRACT

Aplastic anemia is a rare but potentially life-threatening disease that may affect older patients. Data regarding the treatment of aplastic anemia in this ageing population remains scarce. We conducted a retrospective nationwide multicenter study in France to examine current treatments for aplastic anemia patients over 60 years old. Our aims were to evaluate efficacy and tolerance, and to analyze predictive factors for response and survival. Over the course of a decade, 88 patients (median age 68.5 years) were identified in 19 centers, with a median follow up of 2.7 years; 21% had very severe and 36% severe aplastic anemia. We analyzed 184 treatment lines, mostly involving the standard combination of anti-thymocyte globulin and cyclosporine-A (33%), which was also the most frequent first-line treatment (50%). After first-line therapy, 32% of patients achieved a complete response, and 15% a partial response. Responses were significantly better in first line and in patients with good performance status, as well as in those that had followed an anti-thymocyte globulin and cyclosporine-A regimen (overall response rate of 70% after first-line treatment). All treatments were well tolerated by patients, including over the age of 70. Three-year survival was 74.7% (median 7.36 years). Age, Charlson comorbidity index and very severe aplastic anemia were independently associated with mortality. Age, per se, is not a limiting factor to aplastic anemia treatment with anti-thymocyte globulin and cyclosporine-A; this regimen should be used as a first-line treatment in elderly patients if they have a good performance status and low comorbidity index score.

Introduction

Aplastic anemia (AA) affects two to seven individuals per million annually with a higher incidence in Asia than in the west.1–3 Its incidence varies with age, occurring most frequently over the age of 60.4–6 Members of this patient population share specific epidemiological characteristics of the disease, suggesting a different
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pathophysiology to that seen in younger patients. The majority of AA cases in the elderly are idiopathic, since hardly any genetic or viral etiologies are found in this population. However, distinguishing AA from hypocellular myelodysplasia or acute myeloid leukemia (AML) is clearly essential at this age. The gender ratio is also different: although the majority of AA patients under 40 are men, six in 10 patients over the age of 60 are women. From a biological perspective, more mutations are found in AA among the elderly that are potentially associated with adverse outcomes. Conversely, cytogenetic abnormalities are more frequent in younger patients. Moreover, age over 60 years has been identified as an independent risk factor for mortality in AA. Various therapeutic options for AA can be proposed. Immunosuppressive regimens – with anti-thymocyte globulin (ATG) associated with cyclosporine-A (CsA), or CsA alone – have been used to treat AA in the elderly, but have been little studied in this population. ATG-CsA regimen is recommended as first line in patients over the age of 60 with severe or very severe AA. Other options may include androgens, eltrombopag, alemtuzumab, supportive care alone, monitoring with no active treatment, and palliative care; however, none of these has been studied specifically in the elderly. Likewise, data on combined treatments with CsA remains scarce. Eltrombopag has been added to the most recent recommendations for treating AA in the elderly, and may be used as a stand-alone second-line treatment. Androgens, with or without CsA, are recommended as a first-line treatment for non-severe AA. Allogeneic hematopoietic stem-cell transplantation (AH SCT) with a matched sibling donor is recommended as front-line treatment for patients under the age of 40. Recent study suggests that matched sibling donor AH SCT with reduced intensity conditioning may be safely performed after the age of 40 with encouraging outcome. However, in older patients, AH SCT is associated with higher risks, as well as treatment-related mortality and toxicity, even when sibling donors are used. Consequently, AH SCT in patients over the age of 50 is usually only undertaken in very rare and specific cases.

Our study therefore aimed to describe the epidemiology and treatments administered to elderly AA patients in France, as well as to address the factors associated with treatment response and outcome in this population.

Methods

Study Design and Case Detection

We conducted a retrospective study in 19 centers in France on behalf of the French Reference Center for Aplastic Anemia. Cases that fitted the inclusion criteria were identified within a 10-year period (1/1/2007 to 12/31/2016). We started by including all patients whose symptoms and treatments were reviewed monthly in the French Reference Center for Aplastic Anemia. We then asked the pathologist of each center to send us reports concerning patients with aplasia or hypoplasia in their bone marrow biopsy analysis, among whom we identified patients with AA. Before inclusion, all cases were reviewed (AC, FSE, RPL) and data were anonymously collected in a case report form. In accordance with French law, written consent was not required for this retrospective non-interventional study. Patients provided a non-opposition statement.

Population

Patients who were diagnosed with AA by a bone marrow biopsy at the age of 60 or over were included in the study. All histologic diagnoses were made or confirmed in the French lymphopath network, on an expert basis analysis. Patients with toxic or chemotherapy-related aplasia, hypocellular myelodysplasia or AML according to previously published criteria, or paroxysmal nocturnal hemoglobinuria (PNH) without AA, were all excluded.

Definitions

Severe AA (SAA) was defined according to the Camitta criteria as a bone marrow hypoplasia (≤20%) shown by a biopsy with two of the three following criteria: polymorphonuclear neutrophils (PMN) <0.5x10^9/L, platelets <20x10^9/L, or reticulocytes <20x10^9/L. Very severe AA (vSAA) was defined using the same three criteria, but with PMN <0.2x10^9/L. Mild AA was defined by medullar hypoplasia and two associated cytopenias, but no criteria for SAA.

Complete remission (CR) was declared if the patient had the following blood counts without any transfusion: PMN >1x10^9/L, hemoglobin >10g/dL, and platelets >100x10^9/L. Partial response (PR) was defined by the absence of any criterion for either SAA or CR. For patients with mild AA, PR was defined by a significant and stable improvement in the blood counts and no more transfusion requirements, along with no criterion for CR. All other situations corresponded to treatment failure. Responses were considered to be assessable if the treatment line had been initiated more than three months previously, or if a response had occurred before this time.

Treatment lines corresponded to the period between the date of diagnosis for the first line or date of treatment initiation for the following lines and either the date of the next treatment line or the date of patient death. Erythropoietin (EPO) and granulocyte colony stimulating factor (G-CSF) were considered to be supportive care treatments rather than treatment lines.

PNH clones were assessed using flow cytometry analysis on PMNs and monocytes. PNH clone size detection was considered to be positive if above 5%. At inclusion, the Charlson comorbidity index was assessed. Performance status was evaluated at the beginning of each treatment line. Adverse events were assessed using the CTCAEV4.0 scoring system.

Statistical analysis

Statistical analysis is described in the Online Supplementary Material.

Results

We identified 88 patients from the 19 participating centers who fulfilled the inclusion criteria during the study period. Median follow up was 32.1 months (979 days). Our population had a median age of 68.5 years (range 60-89), with 43 women (49%). At diagnosis, the severity of aplastic anemia was mild for 38 patients (43%), severe for 32 (36%), and very severe for 18 (21%); the median Charlson comorbidity index was 2 (range 0-6), with a median performance status of 1 (range 0-3). Population characteristics and main baseline biological results are shown in Table 1. Median blood count values were as follows: PMN 0.705x10^9/L (range 0-7.4); lymphocytes 1.3x10^9/L (0.031-3.94); hemoglobin 8.25g/dL (3.15-6); mean corpuscular volume (MCV) 94fl (80-115); reticulocytes 23.5x10^9/L (0-90); and platelets 10.5x10^9/L (1-82). Bone marrow aspirates were taken from all patients at
diagnosis. In 17 cases (21%), we found minimal signs of dysplasia without fulfilling the criteria for hypoplastic myelodysplastic syndrome. In seven cases (9%), PNH clones were above 5%. Bone marrow biopsies were taken from 88 patients (100%) at diagnosis. Cytogenetic analysis was performed for 78 patients, showing normal results in 80% of these cases, and failure in 11%. Six of these 78 patients (8%) presented cytogenetic abnormalities (Table 1). Overall, the 88 study patients received 184 treatment lines, with a median of two lines per patient (range 1-5). Treatment lines comprised ATG-CsA (33%, including 72% with horse ATG), CsA alone (14%), androgen alone (14%), eltrombopag alone (10%), CsA associated with androgen or eltrombopag (9%), two AHSCTs (1%), and other treatments (19%). For patients who received CsA, median residual dosing of CsA between one and two months after treatment initiation was 200ng/mL (range 42-560). During the first month following initiation of each treatment line, patients received a median of four red blood packs (RBPs) (range 0-26) and four platelet transfusions (range 0-18). Iron chelators were administered in 19% of treatment lines, EPO in 21%, and G-CSF in 23%.

First-line treatment was ATG-CsA for 50% of patients (73% received horse ATG, and 11% a combination of ATG, CsA and eltrombopag), CsA alone for 20%, androgens for 9%, eltrombopag for 3%, and other treatments in 18% of cases. Comparisons of patients treated with ATG-CsA, CsA or other treatments (Table 2) revealed that patients receiving ATG-CsA were significantly younger (66 years, vs. 71.5 vs. 71.5, respectively, P=0.007), more frequently female (61%, vs. 50% vs. 27%, respectively, P=0.02) and had a lower platelet count (8x10^9/L, vs. 12x10^9/L vs. 15x10^9/L, respectively, P=0.025). Interestingly, we found no difference with respect to weight, Charlson comorbidity index score, performance status, disease severity, PNH clones, or myelogram cellularity.

After the 181 assessable treatment lines, 19% achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR. Median time until best response was 151 days (4.9 months). After first-line treatment, 32% of patients achieved CR and 19% a PR.
P = 0.042), eltrombopag (OR 0.12 (0.03;0.54), P = 0.0057) and androgens (OR 0.17 (0.05;0.58), P = 0.0047) were all individually associated with lower response rates than an ATG-CsA regimen (Table 4). The main treatment-associated complications were infections, with 35% of treatment lines complicated by at least one grade-III/IV infection, including 9 deaths (5%), and renal issues, with grade-III/IV acute kidney failure after 29% of treatment lines. Other grade-III/IV complications were hepatic or digestive (11%), cardiovascular (9%), hemorrhagic (9%, including 4 deaths (2%)) and neurological (2%). In comparison with other treatments, ATG-CsA was associated with significantly more infectious (72% vs. 24%, P = 0.0001) and cardiovascular complications (52% vs. 15%, P = 0.01) and acute kidney failure (43% vs. 22%, P = 0.003). Interestingly, patients aged 70 and over receiving ATG-CsA did not seem to experience any more complications than younger patients, and only one patient in this subgroup died during ATG-CsA treatment (Table 5).

Overall survival at three years was 74.7%, with median survival of 7.36 years (Figure 1) and a total of 24 patient deaths from the following causes: nine infections (38%), five deaths in palliative care or after active treatment had finished (21%), four hemorrhagic complications (17%), and six miscellaneous causes. Univariate analysis showed that mortality was significantly higher in patients with Aplastic anemia in the elderly.

Table 2. Population characteristics according to first-line treatment (n=88).

| n (%) or median [IQR] | ATG-CsA (n=44) | CsA alone (n=18) | Others (n=26) | P |
|-----------------------|----------------|------------------|---------------|---|
| Male                  | 17 (39%)       | 9 (50%)          | 19 (73%)      | 0.02 |
| Age (years)           | 66 (62;70)     | 71.5 (65;74)     | 71.5 (68.5;76) | 0.007 |
| Weight (kg)           | 66.5 [61;78]   | 73 [61.7;95]     | 69.5 [65.7;80] | 0.62 |
| Charlson comorbidity index | 1.5 [1.2;2.5] | 2 [1;2]          | 1.5 [1.2;7.5] | 0.96 |
| Performance status    | 1 [0;1]        | 1 [1;1]          | 1 [0;1.75]    | 0.26 |

Table 3. Impact of treatment on outcome (overall response and mortality) after adjustment for treatment line, disease severity and performance status.

| OR (CI95%) | P         | HR (CI95%) | P         |
|------------|-----------|------------|-----------|
| ATG-CsA    | 4.18 (1.93;9.09) | 0.0003 | 0.44 (0.13;1.45) | 0.18 |
| CsA alone  | 0.73 (0.28;1.91) | 0.52 | 2.84 (0.93;8.61) | 0.066 |
| Emtrombopag alone | 0.34 (0.08;1.36) | 0.13 | 0.80 (0.08;7.71) | 0.85 |
| Androgens alone | 0.44 (0.14;1.33) | 0.15 | 1.33 (0.36;4.88) | 0.67 |
| EPO        | 2.05 (0.91;4.6)  | 0.082 | 1.12 (0.35;3.58) | 0.84 |
| G-CSF      | 1.32 (0.59;2.94) | 0.5 | 1.28 (0.50;3.29) | 0.61 |

In analyses, EPO and GCSF were considered to be supportive care treatments rather than treatment lines. ATG: Anti-thymocyte Globulin; CI: Confidence Interval; CsA: Cyclosporine-A; EPO: Erythropoietin; G-CSF: Granulocyte-Colony Stimulating Factor; HR: Hazard Ratio; OR: Odds Ratio.
vSAA (HR 3.02 (1.12;8.12), P=0.029), or with a high baseline Charlson comorbidity index score (HR 1.38 (1.11;1.72), P=0.0043) or performance status (HR 1.77 (1.11;2.83), P=0.017). We also found a trend pointing to an association between age and mortality (HR per year 1.05 (0.99;1.11), P=0.079). Due to the small number of events, our multivariable analysis only included the three most relevant factors. We consequently found that age (OR 1.07 (1.01;1.14), P=0.03), Charlson comorbidity index (HR 1.34 (1.07;1.67), P=0.01) and vSAA (HR 3.67 (1.51;8.91), P=0.004) were independently associated with mortality (Table 6). Regarding the impact of treatment on mortality, Table 3 shows that after adjustment for treatment line, disease severity and performance status, the benefits observed in terms of response with ATG-CsA were not associated with reduced mortality (HR 0.44 (0.13;1.45), P=0.18). Likewise, we found no statistical difference in overall survival between patients who received first-line horse ATG in comparison with rabbit ATG (HR 4.7 (0.4;52.6), P=0.2) or in mortality between patients over 70 years old who received first-line ATG-CsA in comparison with other treatments (HR 0.17 (0.02;1.28), P=0.08).

Discussion

This study focused on current real-life management of AA in the elderly in France. This is, to our knowledge, the largest cohort specifically addressing the question of AA management in the elderly.

Our population comprised patients with a median age of 68.5 years (maximum 89 years) with an even sex ratio, although previous epidemiological studies suggested a feminine predominance in older patients with AA.7 Although patients mostly had SAA or vSAA (57%), nine patients did not require transfusion during the first month following treatment initiation. They had few comorbidities (median Charlson comorbidity index of 2) and were fit (median performance status 1). Of particular notice, although PMN count or hemoglobin may be normal in some patients at diagnosis, all patients had thrombocytopenia (maximum platelets count 82x109/L).

We reported 8% of cytogenetic abnormalities at diagnosis, close to that described in literature (4-5%).11,12,23 We found two Y deletions, an abnormality frequently encountered in the elderly. Others were: one trisomy 8, one split of IgH locus, one deletion 13p and one deletion 4q. Trisomy 8 is known to be seen in AA,25,26 and may be the most frequent cytogenetic aberration in this pathology.11,27 Abnormalities of chromosome 13 have been reported but affecting more often the long arm (13q).28 Finally, deletion 4q has not before been described in this pathology.

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This observational study highlights the great heterogeneity in the choice of treatment in this population. In first line, half of the patients received ATG-CsA, including five with eltrombopag, although combined treatments with eltrombopag in first line is not recommended yet.14 This proportion is consistent with previously reported series.25 One fifth of the patients received CsA alone. Patients receiving ATG-CsA in front line were significantly younger and mostly women. We could not explain this difference in sex ratio. Conversely, other parameters, which could be decisive in treatment choice, like performance status, Charlson comorbidity index or disease severity, did not differ between groups. Analysis of all treatment lines lets us see that most of those were immunosuppressive treatments (58%), mainly ATG-CsA combinations. The majority of ATG-CsA were performed in first line (73%). Patients receiving ATG-CsA after the first line (n=16) were younger (maximum 70 years). Six of them had already received this treatment in first line; while 10 patients had previously received another first line therapy. CsA represented 14% of treatment lines, as androgens. Ertrombopag was given as a monotherapy in 9% of cases. As reported in literature,13 AHSCTs were marginal in this population since two patients received this treatment: the first one for a clonal evolution with 7q- who died from invasive fungal infection; and the second who is alive 36 months after AHSCCT and was refractory to two lines before graft including ATG-CsA. Despite no recommendations, 21% of treatment lines went along with EPO and 23% with G-CSF. EPO and G-CSF were considered to be supportive care treatments and not treatment lines.

The global response rate was 38%, all lines combined. Time to best response was long: 151 days (4.9 months). We observed that in first line, 47% of patients reached response, with 52% of CR. Only 6 patients obtained CR

### Table 4. Impact of treatment on overall response, after adjustment for treatment line, disease severity and performance status (multivariable analysis, with ATG-CsA as a baseline).

| Treatment | OR (CI95%) | P |
|-----------|------------|---|
| ATG-CsA   | 1          | 1 |
| CsA alone | 0.35 (0.13,0.96) | 0.042 |
| Ertrombopag alone | 0.12 (0.03,0.54) | 0.0057 |
| Androgens alone | 0.17 (0.05,0.58) | 0.0047 |
| Other     | 0.24 (0.09,0.63) | 0.0038 |

ATG: Anti-Thymocyte Globulin; CI: Confidence Interval; CsA: Cyclosporine-A; OR: Odds Ratio.

### Table 5. Treatment tolerance comparing ATG-CsA regimens with others.

|                          | ATG-CsA (n=60) | Others (n=124) | P  | ATG-CsA ≥70 years (n=16) |
|--------------------------|----------------|----------------|----|-------------------------|
| Infectious complications | 72%            | 24%            | <0.0001 | 88%                     |
| Cardiovascular complications | 32%        | 15%            | 0.01 | 31%                     |
| Acute kidney failure     | 43%            | 22%            | 0.003 | 50%                     |
| Hemorrhagic complications | 18%            | 15%            | 0.62 | 19%                     |
| Hepatic or digestive complications | 23%        | 19%            | 0.56 | 31%                     |
| Neurological complications | 7%             | 4%             | 0.48 | 13%                     |

no: ATG: Anti-Thymocyte Globulin; CsA: Cyclosporine-A
after first line. The global response rate was higher with ATG-CsA (62% all lines combined, 70% in first line). These results are similar to results in younger patients (global responses of 60% to 80%). In this study, we found no difference in first line ORR between horse and rabbit ATG. Older patients (>70 years) responded well to ATG-CsA, with a global response rate of 81% of (50% CR and 31% PR). Global response after a CsA course was 35%, all lines combined, and 59% in first line, as in a younger population. Responses to eltrombopag (22%) or androgens (21%) were lower. Although defined with different criteria and in a broader population, Lengline et al. found a higher response rate with eltrombopag than us. Baseline Charlson comorbidity index and performance status were associated with a lower response rate. After adjustment for treatment line, performance status and disease severity, we found that ATG-CsA was associated with a better response. Conversely, multivariable analysis showed that patients treated with CsA alone, eltrombopag or androgens were worse responders in comparison with ATG-CsA.

Treatments were well tolerated in this population, with very little treatment-related mortalities, although this should be interpreted with caution due to our retrospective design. Complications were mostly infectious, particularly after immunosuppressive treatments, and especially ATG-CsA, followed by acute kidney failure, almost exclusively seen in patients receiving CsA. Conversely, eltrombopag carries a good tolerance profile in our study. Among patients who died from hemorrhagic complications, none were treated with ATG-CsA, and only 3 in 9 patients who died from infectious complications were under an ATG-CsA regimen. Thus, this treatment, although exposing to more infectious events, rarely conducted to death from infectious origin. Interestingly, patients over 70 years tolerated ATG-CsA as well as younger patients, with one death from sepsis.

Survival was noticeably better than in recently published data with a median survival of 7.36 years and three-year survival of 74.7%. Some of the baseline characteristics were associated with mortality: age, Charlson comorbidity index and vSAA in comparison to SAA and mild AA. The positive impact of ATG-CsA on response rates did not translate into better survival after adjustment for treatment line, performance status and disease severity. Likewise, overall survival did not differ between patients over 70 years who received ATG-CsA in first line in comparison with other treatments as well as in patients receiving horse ATG in comparison with rabbit ATG in first line. It is possible that our cohort was too small to reach significance in survival for patients receiving ATG-CsA and in the other subgroups of our study. Nevertheless, supportive care optimization of hematological patients with cytopenias might also explain the observed survival even in patients with refractory disease. Moreover, death in older patients may be due to causes unrelated to the underlying disease, even in the AA population.

Our study has a number of limitations. Firstly, its retrospective design and case identification strategy may bring some bias, particularly a lack of exhaustivity of our data or patient identifications. We also may have selected more complicated cases by using the data of the French Reference Center for Aplastic Anemia. However, the systematic identification of cases using data from pathologists from each center may have limited this bias. Secondly, the great heterogeneity of treatments in our population did not allow us to conclude on specific regimens like CsA-androgen or CsA-eltrombopag. Specific studies assessing these combinations in this population should be conducted. Thirdly, we found a low rate of clonal evolution with four occurrences. This is less than previously reported, and may be due to the relatively short median follow up of our cohort. Fourthly, multivariable analyses were limited in the number of adjustment variables, to fit with the number of events. However, these variables were selected as the most pertinent and susceptible to bias the univariate analyses results. For the same reason, we were not able to adjust the response or mortality predicting factors on age, although age was associated with survival. We chose to adjust on treatment line, disease severity and performance status because these factors were, for us, the most relevant in this context. Lastly, the retrospective design and data collection of files may limit interpretation of tolerance data, since less serious adverse events may have been neglected in patient reports. Nevertheless, it is probable that most of the serious adverse events have been well reported.

In conclusion, our study shows that current therapeutic choices in elderly patients with AA are very heterogeneous in France, and are not based on objective selection criteria, such as performance status or comorbidities. The impact of the first-line treatment regimen choice in terms of response underlies the need for strong recommendations in this population. Our analysis stresses that some of the patient characteristics are associated with mortality: age, comorbidities, and very severe AA. Given that survival in the elderly is naturally shorter than in younger

Table 6. Impact of baseline characteristics on mortality.

|                                | Univariable analysis | Multivariable analysis |
|--------------------------------|----------------------|------------------------|
|                                | HR (CI95%)           | P                      | HR (CI95%)           | P                      |
| Male                           | 1.74 (0.76;3.99)     | 0.19                   | –                     | –                     |
| Age (per year)                 | 1.05 (0.99;1.11)     | 0.079                  | 1.07 (1.01;1.14)      | 0.03                  |
| Charlson comorbidity index     | 1.38 (1.11;1.72)     | 0.0043                 | 1.34 (1.07;1.67)      | 0.01                  |
| Performance status             | 1.77 (1.11;2.33)     | 0.017                  | –                     | –                     |
| Weight (for each one-kg increase) | 1.03 (1.07)    | 0.059                  | –                     | –                     |
| SAA                            | 1.24 (0.45;3.45)     | 0.68                   | –                     | –                     |
| vSAA                           | 3.02 (1.12;8.12)     | 0.029                  | 3.67 (1.51;8.91)      | 0.004                 |
| PNH clone ≥ 5%                 | 0.66 (0.09;5.5)      | 0.69                   | –                     | –                     |

CI: Confidence Interval; HR: Hazard Ratio; PNH: Paroxysmal Nocturnal Hemoglobinuria; SAA: Severe Aplastic Anemia; vSAA: Very Severe Aplastic Anemia.
patients, overall mortality of AA in elderly is very encouraging. Age, per se, is not a limiting factor to AA treatment with ATG-CsA; this regimen should be used as first-line treatment in elderly patients if they have a good performance status and low comorbidity index score. Among patients with adverse performance status, or comorbidities contra-indicating the use of ATG, CsA alone or in combination may be safely used. Other treatment strategies might be reserved for later courses of treatments. In addition, supportive care may have a great impact on survival in this population. These results require confirmation through prospective data specifically collected in this population with extended follow up.

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