Chapter 3

Consolidation therapy with autologous stem cell transplantation in plasma cell leukemia after VAD, high-dose cyclophosphamide and EDAP courses: a report of three cases and a review of the literature

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Summary
Plasma cell leukemia (PCL) is a rare lymphoproliferative disorder characterized by a malignant proliferation of plasma cells in blood and bone marrow. Treatment of primary PCL has been mostly disappointing. Three patients with primary PCL are described who received high-dose melphalan with autologous peripheral blood stem cell support after vincristine, doxorubicine and dexamethasone (VAD), high-dose cyclophosphamide and etoposide, cisplatinum, dexamethasone and cytosine-arabinoside (EDAP) courses. All patients were in complete remission post-transplantation. One patient relapsed after 3 months; the other patients are still in complete remission, after 14 and 26 months, respectively. These results in conjunction with data from the literature suggest that intensive chemotherapy for PCL is promising.

Introduction:
Plasma cell leukemia (PCL) is a rare lymphoproliferative disorder characterized by a malignant proliferation of plasma cells in blood and bone marrow. Two forms of PCL can be distinguished. The primary form occurs in individuals without preceding Multiple Myeloma (MM) and normally with a rapidly clinical course and a short survival. The second form of PCL typically arises as a late manifestation in individuals with MM in 1-2% of the cases. Additional clinical characteristics of this group include a high frequency of extramedullary disease, severe anemia and thrombocytopenia. Patients treated for PCL with standard alkylating agents and steroids have a short survival, ranging from 2 to 6 months. Vincristine, doxorubicine and dexamethasone (VAD)-based regimens or high dose of an alkylating agent have more promising results and might prolong the long-term survival. Dimopoulos et al studied 27 untreated patients with primary PCL between 1974-1994 and concluded that treatment with standard Melphalan and Prednisolone (M/P) was ineffective, with a median survival of 2.0 months, but more intensive chemotherapy induced responses in approximately one half of the patients, with a median survival of 20.0 months. Patients with secondary PCL have usually received extensive chemotherapy for MM. These patients generally also have a reduced performance status and reduced
bone marrow function. As a consequence intensive chemotherapy is not well tolerated and median survival is 5 months.\textsuperscript{170-172} In the present study we analyzed the results of intensive chemotherapy followed by high-dose melphalan and stem cell support in three PCL patients and compared the results with the literature.

**Patients characteristics**

Three patients with plasma cell leukemia (PCL) were included. Median age was 58 years and all were women. Two patients had Bence Jones (BJ) paraprotein (\(\lambda\) and \(\kappa\) light chain) and one patient had IgG-\(\kappa\). All patients had more than 50% plasma cells in the bone marrow which was positive for CD19, CD38 and BB4 as tested with FACS-analysis (Becton Dickinson, CA, USA; CD19, CD38; Becton Dickinson Immunocytometry Systems, San Jose, CA, USA; BB4; Immuno Quality Products, Groningen, the Netherlands, respectively). Peripheral blood cells contained more than 60% plasma cells in all cases which were CD38/BB4 positive. Two cases had lytic bone lesions. According to the Durie-Salmon staging system, two patients had stage III-A and one patient stage III-B.\textsuperscript{6} The median increase in \(\beta\)-2-microglobulin (\(\beta\)-2-M) found at presentation was 11.0 mg/l (range 7.0-17.6 mg/l, normal 1.0-3.0 mg/l).

Patients were regarded as having achieved complete remission (CR) when no serum M-protein was measurable by immune-electrophresis, no urine M-component measurable (immuno-fixation in concentrated urine/Bence-Jones protein) and less than 5% plasma cells in the bone marrow aspirate (these plasma cells have to be polyclonal by immuno-staining). Patients were in partial remission (PR) if there was a 50% decrease in measurable M-protein or bone marrow infiltration compared with pretreatment values.

**Treatment**

Patients were treated with VAD courses (vincristine (0.4 mg/m\(^2\)), doxorubicine (9 mg/m\(^3\)) intravenously (iv) by continuous infusion every 24 hours for 4 days; dexamethasone (40 mg at day 1-4 and at day 16-20) every 4 weeks until PR was attained or until the paraprotein level plateaued over two successive courses. After a median of 3.7 courses (range 3-5), two patients showed CR with negative immunofix and less than 1% BB4\(^+\) cells in the bone marrow. One patient showed PR with a positive immunofix and 12% BB4\(^+\) cells in the bone marrow. Next, the patients were treated with high-dose cyclophosphamide (6 g/m\(^2\)),
followed by granulocyte-colony stimulating factor (G-CSF) subcutaneously. A median of $17.5 \times 10^6$ CD34$^+$ cells/kg (range 13.9-19.3\times10^6/kg) were collected after one leukapheresis procedure. Response evaluation after EDAP (etoposide 400 mg/m$^2$ iv, cisplatinum 80 mg/m$^2$ iv, 40 mg dexamethasone for 4 days and cytosine-arabinoside 1000 mg on day 5) and before transplantation demonstrated all patients as being in CR with negative immunofixation. Finally, patients were treated with high-dose melphalan (HDM, 200 mg/m$^2$) followed by peripheral blood stem cell infusion. A mean number of $5.5 \times 10^6$/kg (range 4.8-7.0\times10^6/kg) CD34$^+$ cells was reinfused. Mean duration of the granulocytopenia (<0.5\times10^9/l) and thrombocytopenia (<20\times10^9/l) was 14.3 days (range 11-19 days) and 17.7 days (range 15-20 days), respectively. After transplantation all patients were in CR. One patient relapsed 3 months post-transplantation. The other two patients are still in CR after 14 and 26 months. Follow-up of the immunoglobulin levels post-transplantation demonstrated the occurrence of new oligoclonal bands in all three cases. Patient I with a BJ-$\lambda$ paraprotein developed oligoclonality one month post-transplantation, consisting of IgG-$\lambda$ which spontaneously disappeared after 16.0 months (Figure 3.1). After a follow-up of 26 months this patient is still in CR. Patient II, with BJ-$\kappa$, died 3.0 months post-transplantation as a result of tumor progression. Immunofixation demonstrated the development of a new IgG-$\kappa$ paraprotein. All the oligoclonal bands increased in intensity during relapse of the disease (Figure 3.2). Patient III with IgG-$\kappa$ developed oligoclonality 2.0 months post-transplantation consisting of IgG-$\kappa$, IgG-$\lambda$, IgA and IgM. During a follow-up of 14 months the oligoclonality is still present.
Figure 3.1. Transient oligoclonality post-transplantation. (a) Immunofixation at presentation showing \(\lambda\) paraprotein; (b) immunofixation 2 months post-transplantation showing IgG oligoclonality; (c) immunofixation 16 months post-transplantation showing no oligoclonality. SPE = serum protein electrophoresis; IgG = paraprotein IgG; \(a\-\lambda\) = paraprotein \(\lambda\).

Figure 3.2. Oligoclonality post-transplantation. (a) Immunofixation at presentation showing \(\kappa\) paraprotein; (b) immunofixation 2 months post-transplantation showing multiple bands, consisting of IgG, \(\kappa\) and IgA paraprotein. SPE = serum protein electrophoresis; IgG = paraprotein IgG; \(a\-\kappa\) = paraprotein \(\kappa\); IgA = paraprotein IgA.
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Discussion
The present study represents three patients with primary plasma cell leukemia (PCL) treated with high-dose melphalan supported by PSC after induction therapy with VAD, high-dose cyclophosphamide and EDAP courses. CR was attained in all cases. The decline in tumor load was most pronounced after VAD, indicating a very effective chemotherapy regimen for remission induction. Consolidation was further obtained with high-dose cyclophosphamide, EDAP and HDM with peripheral stem cell support. Long term follow-up demonstrated two survivors, whereas one patient relapsed after 3 months.

The optimal treatment for PCL is not well defined. A review of the literature (Table 3.1) demonstrates that patients treated with a single agent with or without prednisone obtain CR in 0-26% of the cases and PR in about 13% of the cases. This includes in total 50 patients. Patients having a response to chemotherapy had a median survival of one year or more and less than one month for patients without a response. Combination therapy with VAD-like regimens resulted in a higher response rate and a longer long-term survival in 66 patients studied. Patients treated according to this regimen demonstrated a CR in 6% and a PR in 42% (range 30-53%).

These data suggest that intensive chemotherapy is most relevant for obtaining long-term survival.\(^{151,173-176}\)

Autologous stem cell mobilization can easily be used in this patient group after remission induction with VAD, providing the opportunity for further dose intensification. Moreover, this approach provides the opportunity to select hematopoietic stem cells by CD34 selection or negative selection with monoclonal antibodies directed to the plasma cells, or a combination of both techniques. Alternatively allogeneic bone marrow transplantation may be used which has the advantage of the graft-versus-myeloma effect.\(^{177}\) However, so far no distinct differences in survival have been seen with either approach.\(^{174}\)

It was noticed that all patients developed oligoclonality post-transplantation. In one patient the oligoclonality had a transient character and disappeared 16 months post-transplantation, while the second patient developed progressive IgG-κ paraprotein with different oligoclonal bands at relapse. The data suggest that the cause of the oligoclonality might vary between the different patients, an imbalance in the B-cell development post-transplantation or a dedifferentiation of the malignant B-cell clone.
In summary, these data suggest that dose-intensification might prolong the survival of patients with PCL.
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References
See page 127-148.