The Safety of Enoxaparin in Patients Older than 60 years with Acute Myelogenous Leukemia or High Risk Myelodysplastic Syndrome Undergoing Chemotherapy

Marwan S Akasheh, MD*                  Majed Abu-Hajir, MD*

Objective: To evaluate the safety of enoxaparin, a Low Molecular Weight Heparin (LMWH) in patients older than 60 years with Acute Myelogenous Leukemia (AML) (Acute Promyelocytic Leukemia (APL) excluded) or high-risk myelodysplastic syndrome (MDS) undergoing chemotherapy.

Methods: The medical records of 178 patients undergoing chemotherapy for the above mentioned conditions at the Medical College of Wisconsin between 1995-1999 were reviewed. A retrospective analysis of 13 patients who were exposed to enoxaparin while undergoing chemotherapy including a group of 12 patients with similar condition but not receiving enoxaparin were analyzed as a control group.

Results: The two groups were compared; the patients who did receive enoxaparin versus those who did not, the median blood and platelets requirements in units were (8 vs.7, p<0.68; 22 vs.18, p<0.04) respectively. There was no significant difference in blood units transfused although more platelet units were transfused in the enoxaparin arm which was statistically significant. One patient on the enoxaparin arm developed shoulder hematoma after a fall. All bleeding episodes in both groups were considered minor. No bleeding related deaths occurred. The mean exposure to enoxaparin was 20.08 ± 1.17 days.

Conclusion: Enoxaparin is a safe anticoagulant when given for a therapeutic indication to patients older than 60 years with a diagnosis of acute myelogenous leukemia or high risk myelodysplastic syndrome undergoing chemotherapy.


Low-molecular-weight heparins have been shown to be both safe and effective for the prophylaxis and treatment of venous thromboembolism. It is uncertain whether anticoagulation can be safely administered in patients undergoing chemotherapy for acute myelogenous leukemia (AML) (APL excluded) or high-risk myelodysplastic syndrome (MDS) since they usually develop severe thrombocytopenia. To study the safety of anticoagulants in this high-risk population, we have chosen a low-molecular-weight heparin (LMWH). Enoxaparin was the most commonly used at our institution. We identified 13 consecutive patients above the age of 60 who received

*Department of Internal Medicine
Division of Hematology/Oncology
Medical College of Wisconsin
Wisconsin, USA.
anticoagulation with enoxaparin while undergoing chemotherapy. They were compared to a cohort of 12 patients with similar diagnoses, undergoing similar treatment but did not receive LMWH or other anticoagulation therapy. Patients were analyzed for the following 30 day outcomes: transfusion requirements, bleeding events and clotting events.

This study was conducted to evaluate the safety of enoxaparin, a Low Molecular Weight Heparin (LMWH) in patients older than 60 years with Acute Myelogenous Leukemia (AML) (APL excluded) or high-risk myelodysplastic syndrome (MDS) undergoing chemotherapy.

METHODS

After reviewing the medical records of 178 patients undergoing chemotherapy for AML and high-risk MDS at the Medical College of Wisconsin during the period 1995-1999, we identified 13 consecutive patients above the age of 60 who received anticoagulation with enoxaparin. All patients with the diagnosis of Acute Promyelocytic Leukemia (APL) were excluded. The chemotherapeutic agents included cytarabine, idarubicin, daunorubicin, mitoxantrone, etoposide, topotecan and fludarabine. Enoxaparin was used either in patients who were already on anticoagulants when their hematological disorders were diagnosed, or those who developed an indication for anticoagulation while undergoing chemotherapy. Enoxaparin was used at the full anticoagulant dose of 1mg/kg administered subcutaneously twice daily. Peak LMWH blood levels were obtained after 2-3 doses of enoxaparin in those patients who had an indication as shown in Table 1.

Table 1. Indications for monitoring LMWH (Anti-Xa assay)

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of &lt; 50-&gt;90 kg.</td>
</tr>
<tr>
<td>Renal impairment Creatinine &gt; 2.0mg/dL.</td>
</tr>
<tr>
<td>When bleeding or clotting occurs in somebody on LMWH.</td>
</tr>
<tr>
<td>Patients with unusual indications i.e. prosthetic heart valves.</td>
</tr>
</tbody>
</table>

Enoxaparin dose was adjusted if blood level was less than 0.5 or more than 1.1 anti-Xa U/ml. LMWH blood levels were performed using a chromogenic anti-Xa assay at the Blood Center of Southeastern Wisconsin, Milwaukee. We identified 13 patients: 4 with high risk MDS and 9 with AML. One patient with high-risk MDS was excluded because of the associated platelet transfusion refractoriness due to HLA-alloimmunization. A control group was selected from patients with similar diagnoses and treatment regimens, provided they survived for at least 30 days after chemotherapy treatment was started in order to obtain adequate transfusion data. No patient in the control group had platelet alloimmunization. Red cells were transfused for a hemoglobin <9 gm/dL, or a hematocrit <0.27 and platelets were transfused for platelets count <10,000 /µL or if the patient is bleeding with platelet counts <50,000µL.
RESULTS

We identified a total of 13 patients: 4 with high-risk MDS, 9 with AML after excluding one patient because of his platelet transfusion refractoriness due to allo-immunization. Twelve patients were evaluated. The indications for the use of enoxaparin in our cohort were: in 7 patients as a substitute to warfarin therapy, which they were already receiving for various cardiovascular indications, 2 patients developed extensive thrombosis at the central venous catheter site (internal jugular vein and subclavian vein). One patient had developed pulmonary embolism (PE) during induction chemotherapy, another patient had PE during consolidation chemotherapy. One patient developed persistent atrial fibrillation during induction chemotherapy. All patients received blood and platelet transfusions at some point during the first 30-day period. None of the patients received recombinant human erythropoietin α (epo) or interleukin-11 (neumega). The incidence of bleeding within 30 days of starting chemotherapy was 100%. All bleeding episodes were considered minor and included the following: petechiae, purpura, ecchymoses, epistaxis, gum bleeding, microscopic hematuria or positive occult blood tests in stools. One patient developed right shoulder hematoma after a fall. Eighty percent of platelet transfusions were received prophylactically, while 20% of all platelet transfusions were administered during minor bleeding episodes. By comparing the two groups, the patients who received enoxaparin versus those who did not, the median (range) number of transfused units of packed RBC was 8 (4-11) vs. 7 (5-11) and the number of platelet units transfused was 22 (18-36) vs. 18 (14-26), respectively (Table 2). Using a non-paired t-test, there was no significant difference in the number of platelet units transfused in the enoxaparin arm (p<0.04) as compared to controls. The mean duration of exposure to enoxaparin was 20.08 ± 1.17 days.

Table 2. Blood product transfusion requirements were significant for more platelets in the arm that received enoxaparin. RBC transfusion requirements were equal in both groups.

<table>
<thead>
<tr>
<th>Blood product requirements</th>
<th>RBC Units Mean (range)/pt.</th>
<th>Platelets Units Mean (range)/pt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on enoxaparin</td>
<td>8 (4-11)</td>
<td>22 (18-36)</td>
</tr>
<tr>
<td>Patients not on enoxaparin</td>
<td>7 (5-11)</td>
<td>18 (14-26)</td>
</tr>
<tr>
<td>t-statistic</td>
<td>0.26</td>
<td>1.3</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;0.68</td>
<td>0.04**</td>
</tr>
</tbody>
</table>

*T-Test for non-paired groups with unequal variance,  
** 2-tailed P values (significant < 0.05),  
pt. = patient

DISCUSSION

The safety and efficacy of LMWH in the prophylaxis and treatment of venous thromboembolism has been well established¹. There is a paucity of data published regarding anticoagulants administered to patients who are pancytopenic and are at an increased risk of bleeding events. Is it safe to administer anticoagulants to a patient who is severely thromboctyopenic? Does this lead to increase in their morbidity and/or mortality? Do they require more blood products compared to a control group undergoing the same treatment? In an attempt to answer some of these questions, we
studied a group of patients who were undergoing chemotherapy for acute myelogenous leukemia and high-risk myelodysplastic syndrome and needed anticoagulation because of indications arising during their treatment or for an already established indication, respectively. We excluded patients with APL (AML FAB-M3) because most of these patients have received All-trans retinoic acid followed by chemotherapy and they received prophylactic heparin, making it difficult to compare their clinical outcome to other AML patients. LMWH was chosen rather than unfractionated heparin, because of the perceived less likelihood of bleeding, possibly secondary to the reduced interference with platelet function. Monitoring of LMWH blood levels (with anti-Xa assay) was done in selected patients, as shown in Table 1. In the enoxaparin group 100% had minor bleeding such as ecchymosis at the injection sites while 70% in the control group had minor mucocutaneous bleeding. There were no episodes of major bleeding in either group. Blood product transfusion requirements do not appear to be drastically increased because of anticoagulation with enoxaparin provided a policy is followed to trigger transfusion at a certain blood counts threshold. None of our patients developed heparin-induced thrombocytopenia, since they all eventually recovered their platelet counts while on enoxaparin. None of the patients treated with enoxaparin died in the initial 30 days, however, our control group was intentionally selected from among those patients who survived the initial 30 days of therapy.

CONCLUSION

We conclude that enoxaparin is a safe anticoagulant in patients above the age of 60 years with AML or high-risk MDS undergoing chemotherapy, even when administered at the full-anticoagulant dose. LMWH blood level monitoring may be helpful in the management of high-risk patients with special indications requiring full anticoagulation.

REFERENCES