Norethisterone Treatment, a Major Risk-Factor for Veno-Occlusive Disease in the Liver After Allogeneic Bone Marrow Transplantation

By Hans Hägglund, Mats Remberger, Sven Klaesson, Berit Lönnqvist, Per Ljungman, and Olle Ringdén

In this single-center study, we retrospectively analyzed incidence and risk factors for hepatic veno-occlusive disease (VOD) in 249 consecutive patients who underwent allogeneic hematopoietic stem cell transplantation between January 1990 and June 1995. Twenty-four of the 249 transplanted patients developed VOD. The probabilities of developing VOD were 17% among women and 7% in men (P = .01). In women treated with norethisterone, the incidence was 27% compared with 3% in women without this treatment (P = .007). One-year survival rates were 17% and 73% in patients with (n = 24) or without VOD (n = 225), respectively. The use of heparin prophylaxis (100 IE/kg/24 hours for 1 month) did not alter the incidence or 1-year mortality of VOD. In multivariate analysis, the following risk factors were significant: norethisterone treatment (P < .001), bilirubin > 26 µmol/L before bone marrow transplantation (BMT) (P = .002), one HLA-antigen mismatch (P = .003), previous abdominal irradiation (P = .02), and conditioning with busulphan (P = .02). Our conclusion is that norethisterone treatment should not be used in patients undergoing BMT and heparin prophylaxis did not affect the incidence or mortality of VOD.

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patients with late disease (≥1 CR/≥1 CP, accelerated phase, or relapse) (P = .06) and busulphan was used more frequently, 44% versus 12% (P < .001), in the nonheparin compared with the heparin group.

Prophylactic treatment. Norethisterone [17-OH-19-nor-17α-pregna-4-en-20yn-3-one] (Primolut Nor; Schering Nordiska AB, Stockholm, Sweden) or Norethindrone (Agyestin; Wyeth-Ayerst, Philadelphia, PA) in USA, 10 mg daily was given from day -7 until platelet recovery (≥30 × 10^9/L) to women (15 to 50 years) to prevent menstrual hemorrhage. Fifty-five of 93 women were treated with norethisterone. Before October 1990, two of 10 adult women received norethisterone, after October 1990, norethisterone had been given to all adult women at risk for menses, 53 of 59 were treated, and six women without menses before BMT were not treated.

Statistical analysis. Analyzed risk factors that might have influenced the development of hepatic VOD are shown in Table 1. VOD within 1 month after BMT was regarded as study outcome. Risk factors significant at the P < .05 level in the univariate logistic regression analyses were entered into a multivariate logistic regression analysis using a backward stepwise procedure. Additional analyses with respect to transplantation-related mortality (TRM), patient survival (PS), etc were analyzed by the life-table method with the log-rank (Mantel-Haenszel) test.12

Table 1. Risk Factors for VOD in 249 Patients Grafted Between January 1990 and June 1995, Univariate Analysis, Logistic Regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient sex female</td>
<td>14(24)</td>
<td>79/225</td>
<td>.03</td>
</tr>
<tr>
<td>Recipient age &gt; 17 years</td>
<td>21(42)</td>
<td>146/225</td>
<td>.04</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>21(46)</td>
<td>186/225</td>
<td>.52</td>
</tr>
<tr>
<td>Advanced disease†</td>
<td>11(46)</td>
<td>83/225</td>
<td>.35</td>
</tr>
<tr>
<td>Recipient CMV seropositive before BMT</td>
<td>18(75)</td>
<td>148/225</td>
<td>.37</td>
</tr>
<tr>
<td>Recipient positive herpes virus serology (3-4)‡</td>
<td>22(92)</td>
<td>164/225</td>
<td>.08</td>
</tr>
<tr>
<td>GVHD prophylaxis with combination therapy‡</td>
<td>24(100)</td>
<td>210/225</td>
<td>.08</td>
</tr>
<tr>
<td>Busulphan</td>
<td>10(42)</td>
<td>63/225</td>
<td>.17</td>
</tr>
<tr>
<td>IVIG prophylaxis</td>
<td>12(50)</td>
<td>99/225</td>
<td>.37</td>
</tr>
<tr>
<td>Liver disease before BMT</td>
<td>4(17)</td>
<td>20/225</td>
<td>.25</td>
</tr>
<tr>
<td>Previous abdominal irradiation</td>
<td>3(12)</td>
<td>8/225</td>
<td>.06</td>
</tr>
<tr>
<td>Infection 1 week before BMT</td>
<td>1(4)</td>
<td>8/225</td>
<td>.88</td>
</tr>
<tr>
<td>Fever 1 week before BMT</td>
<td>12(4)</td>
<td>86/225</td>
<td>.26</td>
</tr>
<tr>
<td>Unrelated transplant</td>
<td>6(25)</td>
<td>66/225</td>
<td>.66</td>
</tr>
<tr>
<td>ALAT &gt; 0.7 µkat/L before BMT</td>
<td>9(38)</td>
<td>84/225</td>
<td>.99</td>
</tr>
<tr>
<td>Bilirubin &gt; 26 µmol/L before BMT</td>
<td>3(12)</td>
<td>3/225</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prophylaxis or treatment started within 1 week before BMT</td>
<td>18(74)</td>
<td>193/225</td>
<td>.17</td>
</tr>
<tr>
<td>Trimethoprim-sulphamethoxazole</td>
<td>13(54)</td>
<td>121/225</td>
<td>.97</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>3(12)</td>
<td>21/225</td>
<td>.62</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2(8)</td>
<td>7/225</td>
<td>.60</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>7(12)</td>
<td>12/225</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>13(54)</td>
<td>42/225</td>
<td>.65</td>
</tr>
</tbody>
</table>

Results

Incidence of VOD. Among the 249 patients, a total of 24 (9.6%) had VOD between January 1990 and June 1995. The probability of developing VOD among female recipients was 17% (n = 14), compared with 7% (n = 10) in male recipients (P = .01) (Fig 1). In women treated with norethisterone, the incidence was 27% compared with 3% (one patient) (P = .007) in women without treatment (Fig 2). In patients receiving a second transplant (not included in the risk factor analysis), the incidence was three of 14 (21%). Twenty-seven patients with bilirubin >34 µmol/L ± one criteria were diagnosed as follows: toxicity, 12; sepsisemia, 5; acute GVHD, 4; acute GVHD/sepsicemia, 3; hemolysis, 1; and unknown, 2 (Table 2).

Clinical features. Of the 24 patients with VOD, 13 were treated with norethisterone and 11 were not treated. Day of diagnosis, liver histology, and outcome in the two groups are given in Table 3. VOD prophylaxis. Among the heparin-treated recipients, 10 of 114 (9%) developed VOD compared with 14 of 135 (10%) in the untreated recipients. The 1-year TRM rates in patients with VOD were 72% and 79% (not significant [NS]), with or without heparin, respectively.

Risk factors for VOD. In the univariate analysis, the following factors were significant: norethisterone (P < .001), bilirubin >26 µmol/L before BMT (P < .001), 1-HLA antigen mismatch (P = .02), recipient sex female (P = .03), and recipient age >17 years (P = .04) (Table 1).

Significant risk factors (P < .05) in the univariate analysis were included in the multivariate analysis. In addition, previous abdominal irradiation (P = .06) and busulphan were included in the multivariate analysis, as both factors have been associated with VOD in previously published studies.2-3 Significant factors were: norethisterone treatment (P < .001), bilirubin >26 µmol/L before BMT (P = .002), 1-HLA antigen mismatch (P = .003), previous abdominal irradiation (P = .02), and busulphan conditioning (P = .02) (Table 4).

For fatal VOD, defined as death within 100 days after BMT in patients with VOD (n = 16), norethisterone (P = .002) and HLA-mismatch (P = .007) were significant in multivariate analysis.

Mortality and VOD. Among 249 patients, the day-100 and 1-year TRM rates were 67% and 81% in patients with VOD (n = 24) as compared with 8% (P < .01) and 17% (P < .001) in patients without VOD (n = 225). One-year observed survival rates were 17%, 44%, and 73% in patients with VOD, with bilirubin greater than 34 µmol/L ± one criteria, or without VOD, respectively. The day-100 and 1-year patient survival among women treated with norethisterone (n = 55) were 78% and 53% as compared with 86% (ns) and 72% (P = .007) in patients (n = 194) without norethisterone during the time period 1990 to June 1995.

Discussion

In this retrospective analysis of risk factors for hepatic VOD, only patients with three clinical features of VOD were included. Twenty-four of 249 (9.6%) BMT patients grafted between 1990 and June 1995 fulfilled the VOD criterion.

Our incidence of VOD, 10%, is comparable to that reported by IBMTR and EBMT. However, this is lower compared with
several other reports, being up to 70% (reviewed in Shulman and Hinterberger13). The reasons for the discrepant frequency of VOD may be due to patient selection, incidence of risk factors, and criteria used for diagnosis.

We found that norethisterone was the most significant risk factor for developing VOD ($P < .001$). Since 1990, 55 of 93 female recipients have been treated with norethisterone (Primolut nor) 10 mg daily, starting 1 week before BMT, to prevent menstrual hemorrhage during the thrombocytopenic period. Among 55 women treated with norethisterone, 13 developed VOD, compared with one of 38 women without treatment.

Three groups have previously reported an increased risk of VOD after BMT among women, with a possible relationship to hormonal treatment.14-16 Ganem et al14 found an incidence of VOD in women of 17.7% and in men, 6.7%. In that study, almost all female recipients received lynesterol, one of its major active metabolites being norethisterone. Progestogens, as well as oestrogens, have been incriminated in the production of venous obstruction, also involving the small hepatic veins.17-18

Cholestatic liver reactions were reported in 5.6% of patients with breast cancer, treated with high-dose gestagen preparations (10 mg × 3 to 4 daily).19 Hepatocellular reactions have also been reported, with use of norethisterone 40 mg daily in 23 of 29 breast cancer patients who developed grade 3 or 4 liver toxicity, according to the World Health Organization (WHO).20 Liver damage from oestrogen is a well-known complication,21 and three recent studies have shown an increased risk of venous thromboembolism among oestrogen users.22-24 The WHO collaborative study of cardiovascular and steroid hormone contraception shows an increased risk of acute myocardial infarction among women with known risk factors and among those who have not been effectively screened, particularly for high blood
pressure and use of combined oral contraceptives. A metabolic conversion from norethisterone to ethinyl oestradiol has been described, which may contribute to the liver toxicity of progestogens. The relationship between VOD and norethisterone may be due to an interaction between norethisterone and other drugs with known hepatotoxicity used for BMT, such as busulphan, cyclophosphamide, methotrexate, and cyclosporin. Superficial venous thrombosis, myocardial infarction, and stroke were found in women with oestroprogestative therapy, related to the dose of progestogens. Norethisterone could therefore increase the risk of microthrombosis in the small hepatic veins. Cholestasis, causing inhibition of bile flow and the biliary excretion of bilirubin and bile salts, may be another explanation of increased toxicity with the use of norethisterone and other drugs. Both hepatocellular and cholestatic reactions could also have a greater effect on a patient previously treated with chemotherapy and/or irradiation, which make the liver more vulnerable to drug toxicity.

Increased bilirubin before conditioning was an important risk factor for VOD. This finding may have been expected, and it suggests that previous cheemoirradiation therapy or infections have damaged the liver in those patients. In patients receiving mismatched bone marrow, an explanation of the increased incidence of VOD may be that a higher dose of cyclosporin was used. Furthermore, an alloimmune GVHD reaction causing a release of cytokines, such as tumor necrosis factor (TNF)-α, may damage endothelial liver cells. In line with this, other groups report less VOD among recipients of autologous, twin, and T-cell–depleted HLA-identical sibling transplants.

Previous abdominal irradiation also increased the risk of VOD, as reported in the EBMT survey. Patients treated with busulphan containing myeloablative regimen developed VOD more often. An increased risk of VOD with the use of busulphan was found in a prospective randomized study comparing busulphan versus TBI as conditioning before BMT. Hepatotoxicity associated with busulphan was also reported after BMT.

We could not confirm previously reported risk factors such as pretreatment fungal infection, pretreatment elevated transaminases, pretreatment fever, antimicrobial or antiviral therapy, and unrelated donor transplants. One reason for the low incidence of VOD in our patients who received transplants from unrelated donors may be that a higher dose of cyclosporin was used in nonnorethisterone-treated women have occurred, we have stopped using this drug to prevent menstruation in women undergoing BMT. We also recommend that other centers stop using norethisterone after BMT.

Because we observed that norethisterone treatment was the strongest risk factor for VOD and no life-threatening bleeding in nonnorethisterone-treated women have occurred, we have stopped using this drug to prevent menstruation in women undergoing BMT. We also recommend that other centers stop using norethisterone after BMT.

| Table 2. Incidence of Increased Bilirubin and VOD Within 1 Month After BMT |
|-----------------------------|-----------------------------|-----------------------------|
| Bilirubin > 34 µmol/L, Bilirubin > 34 + 1 Criterion, VOD | 1990-1995 n = 249 | 51 (20%) | 41 (16%) | 24 (10%) |

Abbreviations: NS, not significant.

<table>
<thead>
<tr>
<th>Table 3. Day of Diagnosis, Liver Histology, and Survival in Patients Who Develop VOD With or Without Norethisterone Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethisterone</td>
</tr>
<tr>
<td>No of patients with VOD</td>
</tr>
<tr>
<td>Day of VOD diagnosis</td>
</tr>
<tr>
<td>Liver histology*</td>
</tr>
<tr>
<td>Centrilobular injury and cholestasis</td>
</tr>
<tr>
<td>100-day survival</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

*Liver histology was evaluable in 10 patients.

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