less known.

We assessed the MTHFR polymorphism in a non-matched case-control study: 107 consecutive thromboembolic patients (deep venous thrombosis and pulmonary embolism), aged 54 years (range 18 to 80) and 200 healthy donors (42 years, range 25 to 54). Venous blood samples in EDTA were obtained for DNA analysis by PCR. The amplified fragments were cut with TaqI which recognized the C→T substitution. Additionally, we measured plasma homocysteine levels in fasting conditions by EIA in all the patients.

The overall frequencies of the three MTHFR genotypes were similar among patients and control subjects. The thermolabile variant (*Val/Val* equivalent to *T/T* homozygosity in 677 position) was found in 13/107 (12.1%) patients and in 20/200 (10%) controls (NSD) with an odds ratio of 1.24 (CI95= 0.6-2.6). The heterozygous *C/T* (*Ala/Val*) frequency was 44%, both in the patients group (47/107) and in the control group (88/200), and the normal homozygous variant (*C/C* or *Ala/Ala*) occurred in 44% of the patients and 46% (92/200) of the controls. After adjustment for FV R506Q and FII G20210A mutations, the estimated risk of venous thrombosis among *T/T* carriers increased up to 1.33 (CI95%=0.6-2.9), but did not reach statistical significance (p=0.50).

Those with abnormal genotype (*T/T*), have higher total homocysteine levels (11.3±4.6 µmol/L) than the others (10.1±6.6 µmol/L in *C/T* and 9.2±5.3 µmol/L in *C/C*) however, without statistical significance (p=0.19).

In conclusion, our data show that homozygosity for the C677T mutation in the MTHFR is not associated with increased risk of venous thromboembolism or, at least, suggest that a big multicenter study would be necessary to obtain a definitive answer.

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Recombinant human tissue plasminogen activator without heparin is effective in the treatment of hepatic veno-occlusive disease

Sir,

We report on 6 patients with veno-occlusive disease (VOD) who have been treated with recombinant human tissue plasminogen activator (rh-tPA) alone, without heparin, at a dose of 50 mg daily for 4 days. Four of them responded. Major bleeding was not observed in any of the patients.

The most effective therapy for VOD after bone marrow transplantation (BMT) has not yet been established. Rh-tPA has been employed both alone and in combination with heparin, but its efficacy remains unclear, and hemorrhagic complications are often described.[1-4] We describe our successful experience in the treatment of VOD with rh-tPA alone.

Our series consisted of 6 patients, (4 males, 2 females), who developed VOD after autologous BMT (5 cases) or syngeneic BMT (1 case). Five patients had multiple myeloma, and one had T-lymphoblastic lymphoma. Median age at BMT was 42 years (range 20-54). Conditioning regimens for transplantation were: Bus 16 mg/kg and Cy 200 mg/kg for 3 patients, Bus 16 mg/kg and melphalan 100 mg/m^2 for 2 patients and melphalan 140 mg/m^2 plus single dose TBI (1000 cGy) for 1 patient. VOD was defined according to the Seattle criteria.[5] The clinical diagnosis of VOD was made at a median of 21 days after BMT (range 15-30). Rh-tPA was administered by 3-4 hours intravenous infusion at a dose of 50 mg daily for 4 days. No patient received heparin in addition to rh-tPA. No patient had renal or pulmonary failure or encephalopathy. The median total serum bilirubin at diagnosis of VOD was 3.14 mg/dL (range 0.87-5.51), while the median serum levels of ALT and AST were 671 U/L and 588 U/L, respectively.

Four patients (66%) responded to rh-tPA, with a complete resolution of painful hepatomegaly or ascites and normalization of hepatic function. Improvement of clinical symptoms was fast, starting

48 h after the beginning of rh-tPA. Recovery of normal laboratory hepatic values was observed within two weeks. Three patients are long-term survivors, in CR. One responder patient died of interstitial pneumonia 35 days after rh-tPA therapy. The two non-responder patients died of multiorgan failure 32 and 40 days after the start of rh-tPA. Life-threatening bleeding did not occur in any patient. Three patients experienced minor bleeding episodes: two in the gastrointestinal tract, and one at CVC cutaneous insertion.

Hepatic VOD is a dramatic toxic complication of hematopoietic progenitor cell transplantation. Once the disease is clinically apparent, few therapeutic approaches are available and the mortality rate is very high.[6] It has been suggested that thrombolytic agents such as rh-tPA, could be therapeutically effective.[2,7] Rh-tPA regimens have been 50 mg/kg/daily by 3-hour i.v. infusion[3] for 4 days, or 0.2 mg/kg/h by continuous i.v. infusion for 5 days.[8] In both cases, rh-tPA has often been associated with low-dose heparin.[4,9] The risk of major bleeding is the principle concern associated with rh-tPA therapy. The largest published series[4]reports that 10/42 (28%) patients receiving both rh-tPA and heparin experienced major bleeding, which was directly fatal in 3 cases and contributed to death in a further 3 patients. It is striking that 9 out of 10 of these patients were on heparin at the time they began to bleed. Our findings suggest that the risk of major bleeding in patients on rh-tPA is substantially reduced in patients receiving rh-tPA alone, with adequate supportive therapy, including massive transfusions of platelets and plasma.

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