Are Circulating Endothelial-Derived and Platelet-Derived Microparticles a Pathogenic Factor in the Cisplatin-Induced Stroke?

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**Background and Purpose**—To evaluate whether cisplatin-induced stroke is mediated by vascular toxicity with release of prothrombotic endothelial and platelet-derived microparticles (MPs).

**Methods**—Endothelial (CD31⁺/CD41⁻), platelets (CD31⁻/CD41⁺) and prothrombotic (Annexin V⁺) circulating MPs were quantified by flow cytometry in 18 patients with cancer, before and 3 days after administration of cisplatin, and compared with 18 healthy controls. Thrombin-antithrombin complex and prothrombin fragments (F₁,₂) were measured as markers of the activation of the coagulation.

**Results**—In patients with cancer, baseline levels of circulating prothrombotic, endothelial and platelet-derived MPs were similar to healthy controls and decreased significantly after administration of cisplatin. High-baseline MP levels were observed in 5 patients who received cisplatin for a second or third cycle. A high-baseline activation of the coagulation was observed in all patients without further increase after cisplatin infusion.

**Conclusion**—Cisplatin treatment is immediately followed by a decrease in circulating levels of endothelial and platelet-derived MPs. However, a transient increase in MPs is observed at the second and third infusion, and this may contribute to the cisplatin-induced stroke.

Key Words: brain infarction ■ cancer & stroke ■ cisplatin ■ microparticles
Results

Eighteen patients (8 women) aged 57±11 years with solid cancer were included. Cisplatin (40 to 150 mg) was administered with etoposide (6 patients), 5-FU (4 patients) and vinorelbine (3 patients). Height patients were having their first cycle of chemotherapy. There was no difference in gender and age between patients and the 18 controls (8 women), age 54±24 years (P=0.67).

Baseline MP were not different between patients and controls (endothelial-derived MPs 435±560/μL versus 460±228/μL, P=0.86; platelet-derived MPs 840±1613/μL versus 1023±810/μL, P=0.67; prothrombotic MPs 1646±2756/μL versus 1612±3664/μL, P=0.97). After cisplatin treatment, patients’ circulating endothelial-derived MPs decreased to 138±133/μL (P=0.003). Platelet-derived MPs s decreased to 231±313/μL (P=0.007). Prothrombotic MPs decreased to 316±499/μL (P=0.02; Figure 1). This decrease was not paralleled by a decrease in blood leukocytes and platelets at day 3. The mean baseline MP levels at different chemotherapy cycles are shown in Figure 2. MP of all origins were higher in the 5 patients at the second and third cycle, compared with the 8 patients at the first cycle (all P<0.07).

Thrombin-antithrombin complex and F1+2 levels showed a slight but nonsignificant increase at day 3 (10.0±8.9 μg/L to 11.6±14.0 μg/L, P=0.57 and 1.31±0.97 nmol/L to 1.41±1.09 nmol/L, P=0.58; Figure 1).

Discussion

This study shows that cisplatin infusion was accompanied by an important and significant decrease of circulating MPs originating from either endothelial cells or platelets. This rapid decrease does not support the hypothesis of a direct cisplatin-induced vascular toxicity mediated by increased circulating levels of prothrombotic MPs, together with activation of the coagulation.

The patients included in this trial are representative of the target population, because cisplatin-induced stroke has been observed in patients aged 25 to 72 years, 2 to 6 days after infusion of cisplatin. The small sample size of our study population may appear as a limitation; however, the decrease in MP was consistent for all MP types.

The decrease in circulating MPs may be explained by direct inhibiting effects of cisplatin on hematopoiesis or dilution by perfusion during chemotherapy. However, both hypotheses are unlikely because numbers of platelets and leukocytes were unchanged at day 3. Alternatively, cisplatin infusion might activate MP clearance. It has been demonstrated that MPs are rapidly removed from the blood by liver Kupffer cells.10 Cisplatin infusion might have increased circulating MP phagocytosis by activating macrophage Kupffer cells, as observed in animal models.11

In conclusion, the present data do not support our first hypothesis that cisplatin-induced stroke is associated with a rapid release of circulating procoagulant microparticles. However, a relation between cisplatin and MP release is not...
definitely ruled out, because we observed high levels of circulating MPs for the patients who were receiving their second or third cisplatin infusion. This observation should be taken with caution but may be relevant because most cisplatin-induced stroke have been observed after the second or third cisplatin infusion. Further studies on the vascular effects of cisplatin are warranted.

Disclosures

None.

References

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