Endogenous serum levels of Thrombopoietin during multiple cycles of chemotherapy

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Objective

To characterize the time course of endogenous Thrombopoietin (TPO) concentration during multiple cycles of conventional chemotherapy

Background

Conventional chemotherapy often induces cumulative toxicity when administered over multiple cycles, especially in the setting of moderate dose intensification (enabled by G-CSF support). The characteristic of the endogenous response pattern of TPO in this setting has not been evaluated in detail so far, but may play a role in planning therapeutic administration of TPO. To learn more about the endogenous TPO response characteristic during chemotherapy induced thrombopenia, we measured platelet counts and TPO levels in patients receiving multicycled myelotoxic chemotherapy.

Patients, Material and Methods

3 patients with non-myeloid malignancies receiving myelotoxic polychemotherapy (standard or intensified) over multiple cycles were evaluated.

Inclusion criteria:

- No signs of bone marrow infiltration by the tumor
- No previous treatment with any cytostatics
- No transfusions during evaluation period

Blood samples were taken in 2-3 day intervals over whole period of chemotherapy

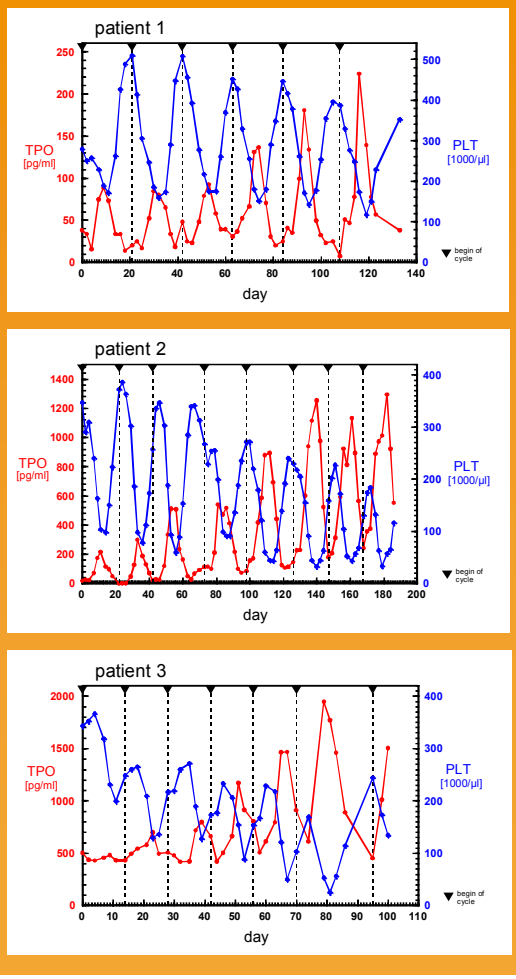
TPO levels were measured using a ready for use sandwich ELISA kit specific for human TPO (Quantikine ®, R&D Systems, Minneapolis, USA)

A cross correlation analysis was performed to characterize the relationship between the time courses of platelets and TPO. By calculating the correlation between both time series for different time lags in between this method is able to identify time lags yielding maximum correlation.

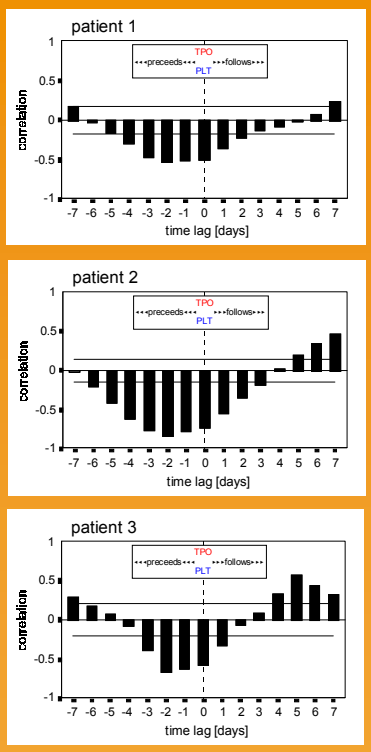
Patient characteristics	Patient 1	Patient 2	Patient 3
Age and sex	57, male	39, male	32, female
Diagnosis and clinical stage (according to Ann Arbor classification)	Non-Hodgkin-Lymphoma, I AE	Hodgkin's Lymphoma, IV BE	Hodgkin's Lymphoma III B
Chemotherapy regimen: Drug, dose, route and days of administration per cycle			
Cyclophosphamide (mg/m²/day) i.v.	750, day 1	1250, day 1	650, day 1
Adriamycine (mg/m²/day) i.v.	50, day 1	35, day 1	25, day 1
Vincristine (mg/day) i.v.	2, day 1	2, day 8	2, day 8
Etoposide (mg/m²/day) i.v.	100, day 1-3	200, day 1-3	100, day 1-3
Prednisone (mg/day) p.o.	100, day 1-5	40, day 1-14	80, day 1-7
Procarbazine (mg/m²/day) p.o.	-	100, day 1-7	100, day 1-7
Bleomycine (mg/m²/day) i.v.	-	10, day 8	10, day 8
G-CSF s.c.	-	5 µg/kg/day, from day 8 to day 14-15	5 µg/kg/day, from day 8 to day 13
Cycle number and duration (intended)	6 cycles à 21 days	8 cycles à 21 days	8 cycles à 14 days

Results

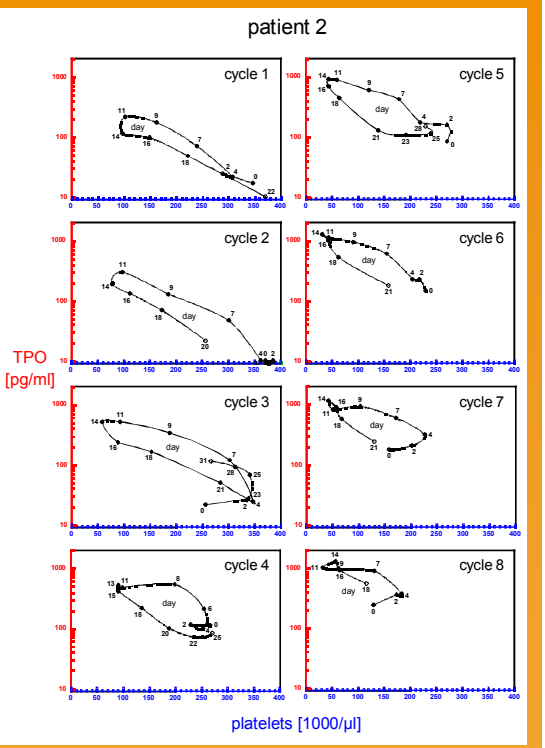
① Time course of platelets and TPO during multiple cycles of chemotherapy



② Results of cross-correlation analysis between platelets and TPO for different time lags



③ Phase-diagram of the relationship between TPO and platelets with time (patient 2)



① Fluctuations of platelets show an increasing toxic response over consecutive cycles with respect to depth of nadirs and peak values on recovery (patient 2 and 3, which received intensified chemotherapy).

Correspondingly, TPO shows an increasing inversed response over consecutive cycles in a quantitative adequate manner.

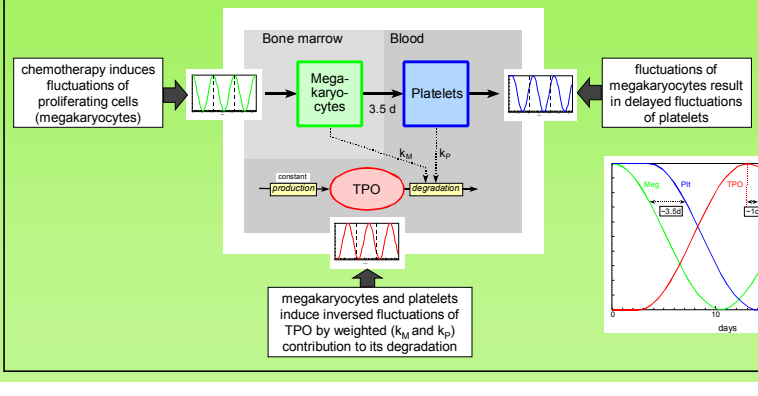
TPO response does not exhaust over multiple cycles of chemotherapy.

② Despite the inverse response of TPO, cross-correlation analysis shows maximum negative correlation between TPO and platelets for a time lag of 1-2 days with the response of TPO preceeding the response of platelets.

③ This phenomenon can be also visualized in a parametric plot of TPO-platelet relationship as a trajectory through time. The trajectory shows a counter clockwise circular orientation in all cycles caused by the phase displacement.

Conclusion

Simple model explanation of the phase displacement between TPO and platelets:



Fluctuations of platelets follow chemotherapy induced fluctuations of megakaryocytes with a certain delay (3.5 days, DASSIN *et al.* 1978).

The inverse response of TPO preceeds the response of platelets.

This phenomenon may be explained by an additional contribution of bone marrow stages (megakaryocytes) to degradation of TPO.

The displacement is determined by the contribution of each compartment to receptor mediated degradation of TPO which itself depends on cell mass and kinetics of receptor-ligand interaction.

Summary

The results of our kinetic study on TPO response pattern during multicycled chemotherapy is in agreement with previous experimental findings that TPO is not exclusively regulated by platelet mass, but also by predecessing cell stages (megakaryocytes).

During intensified multicycled chemotherapy inducing a cumulative toxic response of platelets, TPO response increases in a quantitative adequate manner. However, this increased response is not able to fully compensate the cumulative toxic response.

This data may have to be considered in planning optimal scheduling for exogenous TPO administration. It is hypothesized that TPO administration might be more effective during the first cycles in the multicycled dose-intensified setting.