Results: Dose of busulfan was adjusted in 25 patients (54%). Through levels 25 to 1244 ng/mL, peak levels 849–4586 ng/mL bearing AUC 2225 ng/mL.h–12,818 ng/mL.h were observed. The median total dose of infused drug was 17.52 mg/kg (10.7–22.9). All patients have engrafted, 33 (94%) patients after allogeneic HSCT have reached complete donor chimerism. Acute graft versus host disease grade III-IV manifested in 6 (17%), mucositis grade III-IV was seen in 28 (61%), and VOD was diagnosed in 8 (17%) patients. Defibrotide was administered in 15 patients (therapeutically in 9, as prophylaxis in 8). Neurotoxicity was documented in 2 patients. Relapse occurred in 6 (13 %) patients; 10 (22%) patients died, 5 due to toxicity before day 100 after HSTC, 1 child 15 months after HSCT, 4 due to relapse. 32 children are alive/well (70%).
Conclusion: Parenteral busulfan was used in full myeloablative dose and in combination with other drugs; therefore, toxicity rather than underexposure was our main concern. However, clear correlation between AUC and toxicity was not observed. Because of interindividual differences and changes in pharmacokinetics during the busulfan course, we strongly recommend intensive TDM.
Disclosure of Interest: None declared.

PP114—SUNITINIB DOES NOT REDUCE ENDOTHELIUM-DEPENDENT VASODILATION IN HUMANS

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Introduction: Angiogenesis inhibitors have remarkably improved the outcome of patients with several types of cancer. One of the most reported side effects of angiogenesis inhibitors is hypertension. In a previous study, we showed that infusion of bevacizumab, an antibody directed against vascular endothelial growth factor (VEGF), acutely decreased endothelium-dependent vasodilation in healthy volunteers (A. Thijs et al *Hypertension* 2013;Epub ahead of print). Sunitinib, an inhibitor of tyrosine kinases including the VEGF-receptor, causes cardiovascular side effects similar to bevacizumab. We expected that antagonism of the VEGF receptor and subsequent endothelial dysfunction mediates these cardiovascular adverse events of sunitinib. Therefore, we hypothesized that sunitinib reduces endothelium-dependent vasodilation before hypertension.
Patients (or Materials) and Methods: In patients with metastatic renal cell carcinoma before and 1 week after start of clinically indicated sunitinib (50 mg/d) the endothelium-dependent vasodilator response to intra-arterial acetycholine (ACH, 0.5, 2.0, and 8.0 µg/dL forearm volume/min) and the endothelium-independent vasodilator response to intra-arterial sodium nitroprusside (SNP, 0.06, 0.2, and 0.6 µg/dL forearm volume/min) were assessed with venous occlusion plethysmography. Moreover, blood pressure was measured in supine position at the end of each experiment. For statistical analyses, the FBF ratio (FBF in experimental arm/FBF in control arm) was logarithmically transformed to obtain a Gaussian distribution. Results are expressed as percentage response from baseline (mean [SEM]).
Results: Ten male patients with a mean age of 55 years (range, 24–68 years) were included. No significant changes in FBFresponses before and after start of sunitinib were observed (**Table**). Blood pressure (MAP) before was 101.9 (3.8) mm Hg and 106.1 (2.6) mm Hg after 1 week of treatment (not significant). After 2 weeks of treatment, the blood pressure had increased to 115.8 (4.9) mm Hg ($P < 0.05$).

Table. FBF ratio (% increase from baseline)

	ACH 0.05	ACH 2.0	ACH 8.0	SNP 0.06	SNP 0.2	SNP 0.6
Before sunitinib	246 (100)	1098 (765)	1412 (737)	692 (357)	1184 (552)	3703 (2320)
After sunitinib	201 (76)	252 (72)	542 (144)	378 (158)	1078 (614)	1746 (665)

Conclusion: One-week treatment with sunitinib did not specifically affect endothelium-dependent vasodilation before the development of hypertension.These observations indicate that bevacizumab and sunitinib differ with respect to their vascular actions in humans in vivo and suggest that other factors contribute to the development of hypertension in response to sunitinib rather than endothelial dysfunction.
Disclosure of Interest: None declared.

PP115—LOSS OF NFKB ACTIVITY DECREASES HEAT SHOCK PROTEIN LEVELS IN PANCREATIC CANCER CELLS

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Introduction: Pancreatic cancer patients have an overall 5-year survival of <5% worldwide, due to both late-stage diagnosis and lack of treatment options. Therefore, the development of novel chemotherapeutic modalities based on a deeper understanding of the disease is essential for improving patient survival. We have recently developed Minnelide, a novel prodrug of the diterpene triepoxide, triptolide, as a novel chemotherapy against pancreatic cancer. Although Minnelide has shown great promise in preclinical studies using various animal models of pancreatic cancer, its mechanism of action remains unclear. NFkB activity and HSP70 expression are pro-survival pathways upregulated in pancreatic cancer. Previous studies from our group and others have shown that triptolide decreases NFkB activity. We have also shown that triptolide-mediated loss of HSP70 results in pancreatic cancer cell death. However, it is unclear if down-regulation of both HSP70 and NFkB are part of sequential or parallel pathways. We hypothesized that a triptolide-mediated decrease in NFkB activity results in down-regulation of HSPs, resulting in cell death.
Patients (or Materials) and Methods: Tumor volume evaluation: 5×10^5 MIA PaCa-2, S2-VP10, S2-013, AsPC-1, or KPC (derived from KRasG12D; Tp53R172H; Pdx-1 Cre animals) pancreatic cancer cells were injected subcutaneously into animals and tumor volume measured 28 days postinoculation. RNA and Protein: RNA levels were assessed using real-time qPCR. Protein levels were evaluated by western blotting. NFkB activity: NFkB activity was measured using a p50 binding assay kit (Pierce).
Results: Using either KPC cell lines, known to mimic human pancreatic cancer progression, or human tumors, we show that the KPC cell line is the most aggressive of all cell lines tested in its ability to form tumors. The KPC cell line also possesses the highest NFkB activity of all cell lines tested, accentuating the importance of NFkB in pancreatic cancer. To evaluate the mechanism of action of Minnelide, we used 2 human tumor-derived pancreatic cancer cell lines: MIA PaCa-2, derived from a primary tumor, and S2-VP10, derived from a liver metastasis. In both of these cell lines, triptolide treatment decreases RNA and protein levels of p50 and p65, as well as NFkB