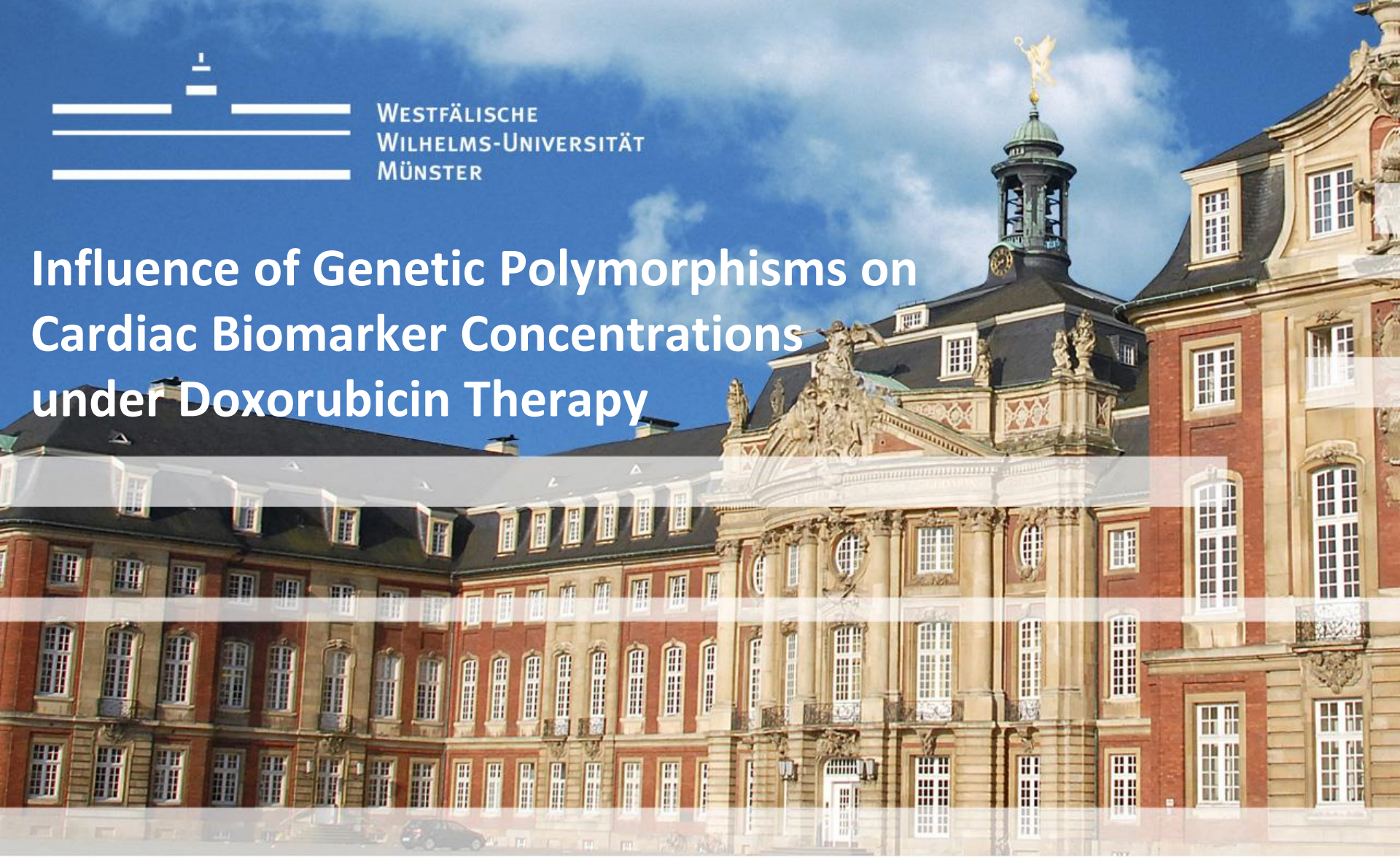

Westfälische Wilhelms-Universität Münster

Influence of Genetic Polymorphisms on Cardiac Biomarker Concentrations under Doxorubicin Therapy

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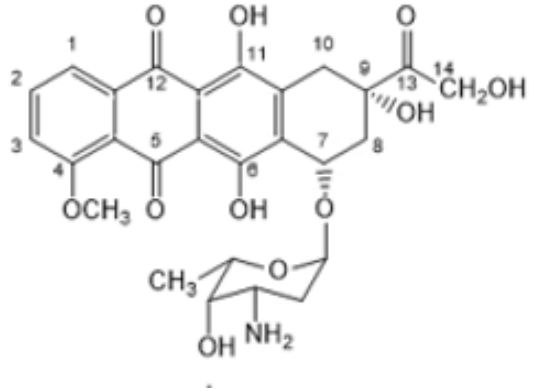
Farina Hellmann

PharmaCampus

Doxorubicin



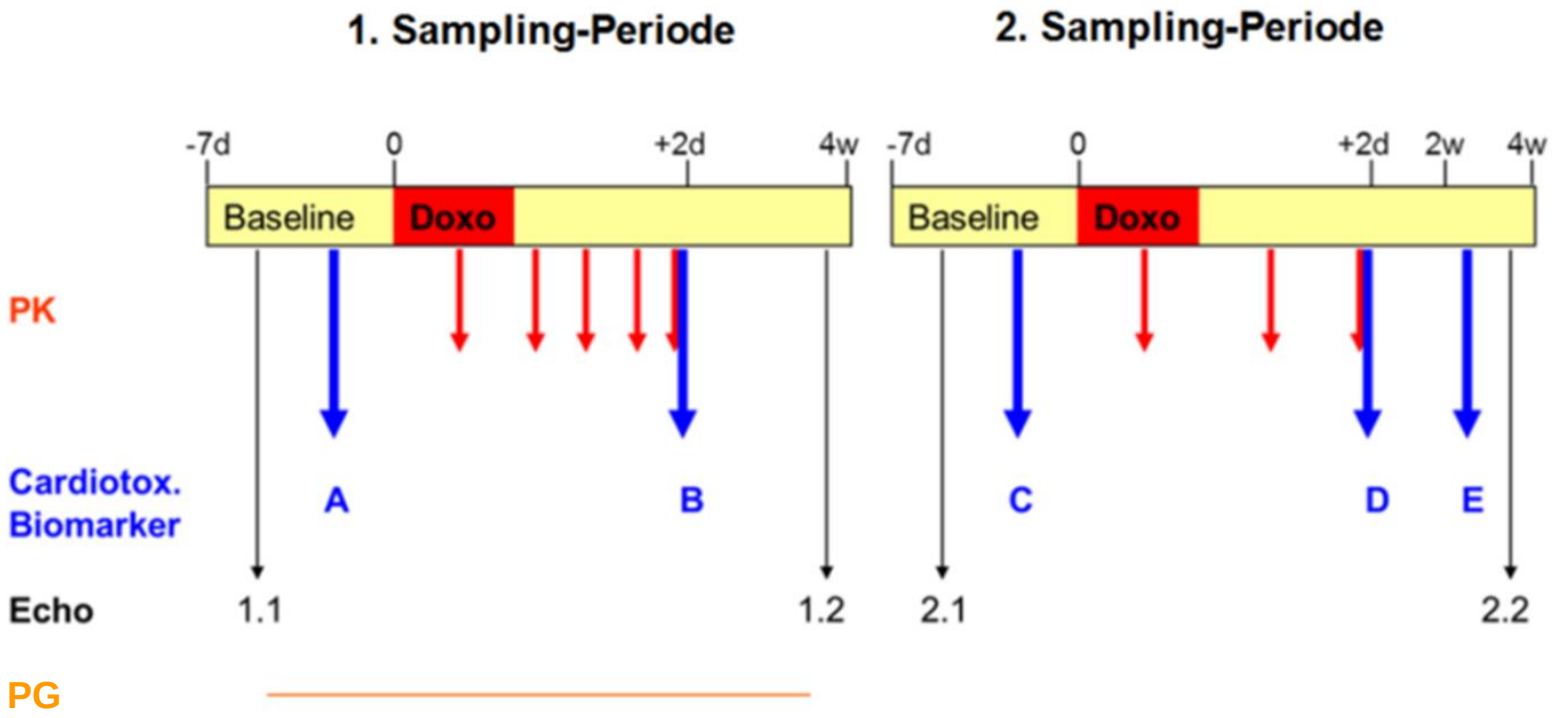
- Important drug in the treatment of paediatric cancers[1]
- Use is limited by cardiotoxic side effects[1]
- Echocardiography is the standard method for monitoring chemotherapy related cardiotoxicity[2]
- Cardiac biomarkers can be beneficial for monitoring[2]
- Genetic polymorphisms could influence the pharmacokinetics and pharmacodynamics of doxorubicin[3]
- **Is there an influence of genetic polymorphisms on the cardiotoxicity of doxorubicin?**

1. Kremer, L.C.M., et al., Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. Annals of Oncology, 2002. 13(4): p. 503512.
2. Christenson, E.S., et al., Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity. Clinical Biochemistry, 2015. 48(4-5): p. 223-235.
3. Jamieson, D. and A.V. Boddy, Pharmacogenetics of genes across the doxorubicin pathway. Expert Opinion on Drug Metabolism & Toxicology, 2011. 7(10): p. 1201-1210.

Study design

- **Phase II pharmacokinetic study** (EudraCT number: 2009-011454-17; short title: doxo)
- **Primary objective:**
  - Assess age-dependency in pharmacokinetics of doxorubicin in paediatric patients with solid tumours and leukaemia
- Carried out by the **European Paediatric Oncology off-patent Medicines Consortium**
- **20 clinical centres involved** (6 in Germany, 6 in France, 5 in UK and 3 in Italy)
- **101 patients** (0-17 years) were included

Study design



Natriuretic peptides: proANP, BNP and NT-proBNP

Cardiac troponins: cTnT and cTnI

Genetic polymorphisms

Enzymes

- **NADPH-quinone-oxidoreductase**
  - NQO1 - C609T - rs1800566
  - NQO2 - rs1143684
  - NQO2 - Insertion/Deletion
- **Carbonyl-reductase**
  - CBR1 - rs9024
  - CBR3 - rs8133052
  - CBR3 - rs1056892
- **Uridin-diphosphate-glucuronyl-transferase**
  - UGT2B7 - hCV32449742 - C_32449742_20

Transport proteins

- **ABC-transport proteins**
  - ABCB1 - rs1128503
  - ABCB1 - rs2032582
  - ABCB1 - rs1045642
  - ABCC1 - rs4148350
  - ABCC1 - rs246221
- **SLC-transport proteins**
  - SLC22A16 - rs723685
  - SLC22A16 - rs12210538
  - SLC22A16 - rs714368
  - SLC22A16 - rs6907567
  - SLC28A3 - rs7853758

Is there an influence of genetic polymorphisms on the cardiotoxicity of doxorubicin?

- IBM SPSS® *Statistics* software
- Not normally distributed data
- Non-parametric test

Kruskal Wallis test

with pairwise comparison by Dunn-Bonferroni

Rise in serum biomarkers vs. SNP`s:

Results of the Kruskal Wallis test

biomarker	time point	SNP	statistic			
			N	df	chi²	p
BNP	A	*ABCB1 - rs1128503*	88	2	7,368	0,025
	B	*SLC22A16 - rs714368*	88	2	6,808	0,033
		SLC22A16 - rs6907567	88	2	6,808	0,033
	C	*CBR3 - rs8133052*	88	2	9,404	0,009
proANP	C	*NQO2 - insertion/ deletion*	86	1	6,815	0,009
	E		81	1	4,670	0,031
		ABCC1 - rs4148350	86	1	4,474	0,034
cTnT	A		91	1	7,873	0,005
	B		90	1	4,776	0,029
	D		90	1	3,842	0,050
NT-proBNP	A		91	1	3,901	0,048
		ABCB1 - rs1045642	90	2	7,650	0,022
	D	*SLC28A3 - rs7853758*	89	2	7,069	0,029

Two genotypes

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Rise in serum biomarkers vs. SNP`s

Significant results for 7 of 17 genetic polymorphisms:

- ABCB1 rs1128503 and rs1045642
- ABCC1 rs4148350
- SLC22A16 rs714368 and rs6907567
- CBR3 rs8133052
- NQO2 Insertion/Deletion

Conclusion

- Various genotypes of genetic polymorphisms could lead to differences in the concentration of cardiac biomarkers
- So there seem to be an influence on the development of anthracycline-induced cardiotoxicity
- Further trials are necessary to assess the use of genetic markers for monitoring chemotherapy related cardiotoxicity

More information about the doxo study

Krischke, M., et al., Pharmacokinetic and pharmacodynamic study of doxorubicin in children with cancer: results of a "European Pediatric Oncology Off-patents Medicines Consortium" trial. Cancer Chemother Pharmacol, 2016. 78(6): p. 1175-1184.

open access

Voller, S., et al., Towards a Model-Based Dose Recommendation for Doxorubicin in Children. Clin Pharmacokinet, 2016. *open access*

Voller, S., et al., Age-Dependent Pharmacokinetics of Doxorubicin in Children with Cancer. Clinical Pharmacokinetics, 2015. 54(11): p. 1139-1149.

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