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Primäre Thromboseprophylaxe bei uroonkologischen Tumorpatienten

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CDFANKHAUSER

Organizer

1. Consequences of VTEs
2. Incidence of VTE
3. Efficacy of primary thromboprophylaxis
4. How to balance risk benefits in testis, urothelial and other GU cancers

Consequences of VTE

1. **Thrombosis in leg**: Post-thrombotic syndrom: pain, leg ulcers
2. **Pulmonary embolism**: death, chronic thromboembolic pulmonary hypertension (CTEPH)
3. **Need for full-anticoagulation** > 6 months or forever

   Risk of bleeding during full anticoagulation ~4%, often requiring surgical, endoscopic or endovascular procedures

Incidence of VTE

- Cancer and chemotherapy ↑ VTE prevalence
- Khorana score
  - Site of cancer (GU=1), platelets, hemoglobin, WBC, BMI
  - low number of events
  - adenocarcinomas, lymphomas, sarcomas (((GU cancers)))

Randomized trials for primary VTE prevention

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	Cassini	Avert	SAVE-ONCO	PROTECHT	PRONOMOS

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Sample size	500 some GU	1000 some GU	3200 some bladder	1000 No GU	3604 ortho

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Sample size	500 some GU	1000 some GU	3200 some bladder	1000 No GU	3604 ortho
VTE -Control -Intervention					
Relevant bleeding -Control -Intervention					
Major bleeding -Control -Intervention					

Randomized trials for primary VTE prevention

	Cassini	Avert	SAVE-ONCO	PROTECHT	PRONOMOS
Sample size	500 some GU	1000 some GU	3200 some bladder	1000 No GU	3604 ortho
VTE -Control -Intervention	HR 0.41 10% placebo 4% rivaroxaban	HR 0.66 8% placebo 6% rivaroxaban	HR 0.36 3.4% placebo 1.2% semuloparin	 3.9% placebo 2.0% nadroparin	RR 0.25 1.1% enoxaparin 0.2% rivaroxaban
Relevant bleeding -Control -Intervention	HR 1.34 2.0% placebo 2.7% rivaroxaban	HR 1.28 5.5% placebo 7.3% apixaban	HR 2.41 2.0% placebo 2.8% semuloparin		 0.7% enoxaparin 0.6% rivaroxaban
Major bleeding -Control -Intervention	HR 1.96 1.0% placebo 2.0% rivaroxaban	HR 0.41 1.8% placebo 3.5% apixaban	HR 1.05 1.0% 1.2%	 0.7% 0%	 0.7% enoxaparin 0.6% rivaroxaban

Summary primary prevention accross all studies

- Heparins (LMWH) or Direct Oral Anticoagulant (DOAC)
  - decrease VTEs ~ ↓50%
  - Increase risk of bleeding ~ ↑ 0-100%

ASCO recommendation

- VTE prophylaxis during chemotherapy in patients with high risk of VTE and low risk of bleeding
- LMWH or Direct Oral Anticoagulant (DOAC)

Risk benefit of VTE prophylaxis

VTE incidence * efficacy of VTE prophylaxis **>** **Bleeding incidence * risk of bleeding**

10%	* 0.5	= 5%	1%	*2	=2%
5%	* 0.5	= 2.5%	1%	*2	=2%
-> Hospitalised patients					
2%	* 0.5	=1%	1%	*2	=2%

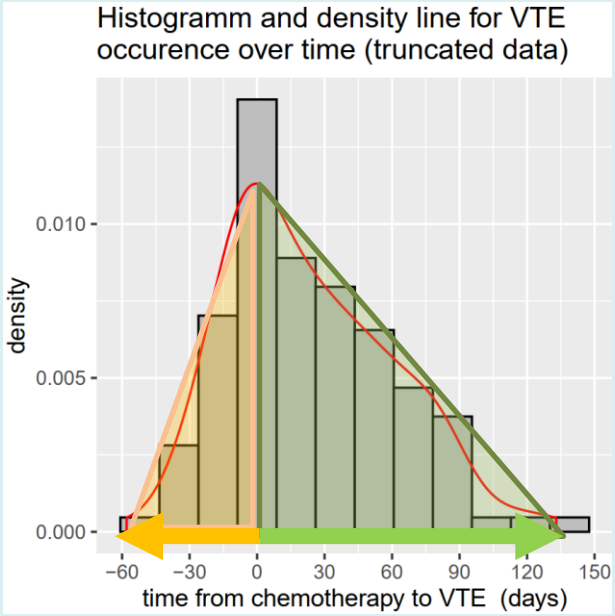
Fankhauser et al, Eur Urol, 2019

Testis cancer

- 1120 men with metastatic germ cell tumors undergoing first-line chemotherapy

Fankhauser et al, Eur Urol Focus, 2020

VTE at any time	121 11%



Biology?

Treatment?

VTE before chemotherapy	49 4%

Risk factors: RPLN >3.5cm, Khorana score

VTE during or after chemotherapy	72 7%

Risk factor: use of a venous access device

Fankhauser et al, Eur Urol Focus, 2020

Conclusions based on thromboembolic incidence in testis cancer

- High VTE incidence before and during/after chemotherapy
    1. Check CT for asymptomatic VTE?
    2. Screening US legs before chemotherapy?
    3. If, start prophylaxis early
    4. Only modifiable risk factor is the use of a **central venous access device**

EAU guideline recommendation	Strength rating
Balance the individual patients' potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumors	Weak

Fankhauser et al, Eur Urol, 2021

EAU guideline recommendation	Strength rating
Balance the individual patients' potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumors	Weak
Avoid use of a central venous-access device during first-line chemotherapy whenever possible	Weak

Fankhauser et al, Eur Urol, 2021

Urothelial cancer

	VTE
Neoadjuvant chemotherapy	8-35% before cystectomy
First-line gem cis	10%
Immunotherapy	6%
Adjuvant gem cis UTUC	6%

Schomburg et al, Urology, 2018

Birtle et al, Lancet, 2020

LUKS standard of care: Prevent VTEs

-VTE prophylaxis in all patients undergoing chemotherapy for urothelial cancer

-Prevent anemia in all patients undergoing neoadjuvant chemotherapy

Urothelial cancer

Anemia during neoadjuvant chemotherapy
-Increases perioperative morbidity

LUKS standard of care: Prevent anemia
-Ferinject if ferritin ≤ 450 pmol/L or ≤ 675 pmol/L with transferrin saturation ≤ 19%
-Folic acid, VitB12
-Hb ≤ 105 g/L: ?rHuEPO 40,000 U once weekly

Prostate cancer

	VTE	
Surgery	0-2%	Fankhauser et al, Eur Urol, 2020
Radiotherapy	2-3% (within 10y)	Deka et al, Prostate, 2019
ARASENS	0%	Smit et al, NEJM, 2022

Renal cell cancer

	VTE
Surgery	1%
Lenvatinib plus Pembrolizumab or Everolimus	0%

Jordan, WJUR, 2017

Motzer et al, NEJM, 2021

Summary

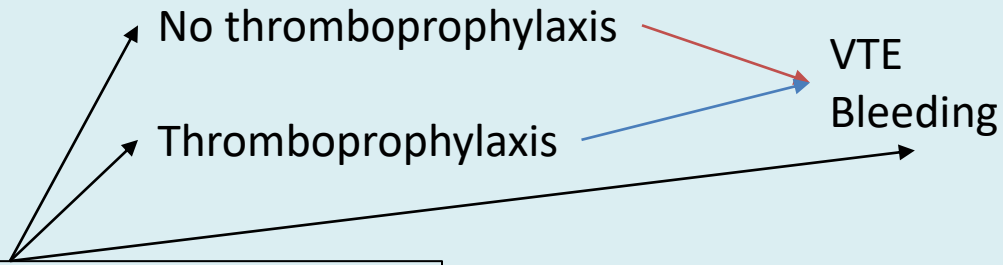
- **High** VTE incidence during chemotherapy in
  - germ cell cancer + cisplatin
  - urothelial cancers + cisplatin
- Thromboprophylaxis decreases risk of VTE but increases risk of bleeding
- VTE prophylaxis= standard of care in
  - germ cell cancer + cisplatin
  - urothelial cancers + cisplatin
  - Regardless of Khorana score
- Avoid central venous access devices
- Screen and treat anemia in patients (esp. if scheduled for surgery)

Acknowledgements

- Stefan Aebi, Beat Müller, Philipp Niederberger, Sandra Schmid
- Mattias Casutt
- Walter Wuillemin

Additonal slides if needed

Retrospective analyses



Confounders
Central venous access device
Retroperitoneal lymph nodes size
Khorana score
IGCCCG intermediate/poor risk
LDH
AFP
Body surface area >1.9 m2, Weight >70kg, BMI (expert opinion)
Febrile neutropenia
History of previous VTE (expert opinion)

Men with several risk factors have a higher risk for VTE/bleeding
are more likely to receive thromboprophylaxis= CONFOUNDING

Fankhauser et al, Eur Urol, 2020

Simulation

VTE during /after chemotherapy	%VTE
All patients	7%
No venous access device	5%
Venous access device	10%

Bleeding
< 1%

HR 0.66*

*conservative efficacy from AVERT

Risk factors	NNT
All patients	45
No venous access device	55
Venous access device	31

Bleeding NNH
186

(number of bleedings because of full-anticoagulation after VTE not included)

Fankhauser et al, Eur Urol, 2020