

Venous Thromboembolism and Oncology Patients

Update 2000

Coagulation and Cancer

- Tumor cell release of cysteine and serine proteases, e.g. Xase in GI malignancies
- Tumor cells release tissue factor to activate extrinsic coagulation → DIC
- Tumor cells activate platelets, mediating formation of heterotypic tumor cell-platelet aggregates
- von Willebrand factor interacts with laminin, tumors, platelets

Coagulation and Cancer: New Concepts

- TF-bearing TC's induce platelet VEGF release; mediated by thrombin; blocked by Anti-GP IIb/IIIa & Hirudin.
- ↑ Expression of PAI-1 is a poor prognostic indicator for overall survival in breast cancer.
- ↑ Expression of TM ↓ proliferation & Met potential of transfected esophageal and pancreatic CA cell lines; ↓ TM expression in primary breast CA predictive of metastases to LN's.

Heparin and Cancer

- Heparin possesses activities unrelated to anticoagulation
- In 1930, heparin first noted to inhibit growth of tumors implanted in rats (Groener)
- Heparinized rats have ↓ metastases and ↑ survival post Walker 256 lung tumor (Terranova, 1952)
- Chemically modified UFH and LMWH inhibit experimental mets and led to long-term survival in some animals; anticoagulant properties unimportant (Sciumbatta, 1996)

Heparin and Cancer

- In experimental studies, LMWH and LMW Heparan sulfate suppressed angiogenesis (rat cornea post chemical cauterization); UFH stimulated angiogenesis (Lepri, 1994)
- Heparanase inhibiting species of heparin inhibit tumor metastasis in experimental animal models; anticoagulant potential unimportant; LMWH = UFH (LaPierre, 1996; Voldavsky, 1994)

Heparin and Cancer

- Degree of anticoagulation may not affect cancer survival & metastatic potential in animal models.
- Data discrepancies due to differences in animal species, tumor cell lines (clonal variability), experimental designs, etc.
- Difficult to extrapolate heparin animal data to develop rational trial design in cancer patients

Retrospective Studies: Heparin and Cancer Survival

- Kakker et al, 1995
 - 331 patients for cancer surgery
 - 163 received low-dose UFH
 - > 3 year follow-up
 - Mortality: 7.6% versus 12.5% ($p=0.0005$) over 3 years
 - Disease dissemination (Mets) = 24.4% vs. 9.2% for UFH
 - Tumor type and stages not reported

Retrospective Studies: Heparin and Cancer Survival

- Siragusa et al, 1996
 - Meta-analysis of 13 trials of DVT with UFH vs LMWH
 - Unselected patients
 - Benefit when > 15 days of treatment
 - 67% ↓ RR mortality with LMWH at 3 months
 - Most patients died after D/C LMWH

Retrospective Studies: Cancer Survival and Heparin

- *Hettiarachchi et al (Thromb Haemost, 1999)*
 - Meta-analysis of 22 randomized clinical trials: sq fixed dose LMWH vs IV adj dose UFH X 5-10 d as initial treatment of VTE in CA pts followed by >3 mos
 - 405/629 CA pts analyzed (200/LMWH, 205/UFH)
 - $\approx 40\%$ \downarrow 3-month mortality in favor of LMWH;
 - (34/200 [10.7%] LMWH vs 44/205 [21.1%] UFH)
 - Same result in sub-cohort analysis adjusted for age, gender, and primary; \uparrow mortality difference when tumor stage, histology, duration, and sites of metastasis considered

Prospective Studies: Heparin and Cancer Survival

- Lebeau et al, 1994
 - 277 patients with SCLC received chemotherapy ± adjusted dose SQ UFH X 5 days
 - Randomized, prospective, multicenter study
 - CR: 37% (UFH) vs 23% (p=0.004)
 - Median Survival: 317 (UFH) vs 261 days (p=0.01)

Prospective Studies: Heparin and Cancer Survival

- Von Templehoff et al, 1997
 - Perioperative DVT prophylaxis in 60 ovarian cancer patients
 - +6 cycles of chemotherapy
 - UFH vx LMWH administered for 7 days
 - Double-blind, randomized study
 - At median follow-up of 26.5 months, 21.4% deaths (LMWH) vs 37.5% (UFH)
 - Number of patients too small, $p=0.26$

Prospective Studies: Heparin and Cancer Survival

- *Von Tempelhoff et al (Thromb Haemost, 1999)*
 - Double-blind randomized prospective trial with LMWH vs UFH in 324 GYN CA pts during primary CA surgery
- Certoparin 3000 anti-Xa U/d sq (n=160) vs UFH 5000 U sq tid (n=164); tx begun 4 hr pre-op and continued for 7 days
- At 650 days follow-up: mortality ↓ for LMWH (5.7% vs 15.6%, p=0.005); no differences > 3yrs.
- Advantages observed only in ovarian and uterine CA but not breast CA

Difficulties in Trial Design For Heparin Benefit

- Many are retrospective/meta-analysis
- Effect of LMWH on CA survival in humans has not been investigated as a primary objective in prospective, well-designed trials
- Many are underpowered
- Tumor types/stages/aggressiveness/chemotherapy regimens are not standardized
- Variable thoroughness in search for asymptomatic VTE

Difficulties in Trial Design For Heparin Benefit

- No standardized use of adjunctive modalities, i.e., compression boots, heparin flushes through lines, ASA, calcium channel blockers, etc....
- No comparisons between LMWH preparations/regimens
- Few Autopsies
- Coag abnormalities: cause or effect of VTE?
- Populations at different risks for VTE, i.e., Factor V Leiden frequency: whites>blacks>Asians

LMWH > UFH

In Cancer Treatment

- LMWH: ↓ platelet activation & aggregation
 - ↓ stimulation of osteoclasts → ↓ osteoporosis
 - ↑ stimulatory effect of megakaryocytes →
↓ chemo-induced thrombocytopenia
 - ↑ inhibitory effect on angiogenesis
 - Inhibits FGF- β mediated proliferation of human colon cancer cell lines

Warfarin and Cancer

- *Mauer et al, 1997*
 - SCLC patients received 3 cycles ACE; 2 cycles PCE with concurrent XRT; randomized \pm warfarin
 - Median survival: 33 mos with warfarin vs 13.7 mos ($p=0.05$)
 - No difference in dissemination, patterns of relapse or response rates

Warfarin and Cancer

- *Bona et al, 1995*
 - 44 CA patients versus 64 controls; non-randomized
 - INR 2-3 for previous VTE
 - No difference in rethrombosis or major/minor bleeds
 - % INRs in therapeutic range: CA=43.3%, con=56.9% (p=0.0001)

Warfarin and Cancer

- Falanga et al, 1998
 - 32 breast CA patients (Stage IV) randomized to warfarin 1 mg qd x 6 weeks, then adjusted to INR 1.3 - 1.9 versus placebo at start of chemotherapy until end of chemo
 - Markers of thrombosis measured
 - TAT, d-Dimer, Factor VII, P F₁₊₂
 - p=0.01 after 4th cycle, 2 DVT in placebo arm

Warfarin and Cancer

- Historical Reference: Stage 2 breast cancer
 - Recurrent Thrombosis = 5%
 - ↑↑ risk with TAM + CF/CAF
 - Up to 40% failure of warfarin in Trousseau's Syndrome

Enoxaparin in VTE Treatment

Study CPK 2091

- Summary of VTE Recurrence by Subgroups

	Heparin n/N (%)	Enoxaparin BID n/N (%)
• All Patients	17/254 (6.7)	13/247 (5.3)
• Presence of Cancer	9/57 (15.8)	6/46 (13.0)
• Gastrointestinal	3/11 (27)	2/9 (22)
• Pulmonary	2/5 (40)	2/6 (33)
• Lymphoma	2/5 (40)	1/3 (33)
• Prostate	1/9 (11)	0/5 (0)
• Brain	1/6 (17)	1/5 (20)

Enoxaparin in VTE Treatment

	Heparin	Enox QD	Enox BID
•	N=290	N=298	N=312
•	n/N (%)	n/N (%)	n/N (%)
• All Patients	12/290 (4.1)	13/298 (4.4)	9/312 (2.9)
• Recent CTX/RTX	1/24 (4.2)	1/30 (3.3)	2/28 (7.1)
•		[-3.8%;12.2%]	[-9.5%;15.4%]
• Presence of Cancer	3/45 (6.7)	6/49 (12.2)	3/49 (6.4)
•		[-7.8%;17.7%]	[10.4%; 9.8%]
• Gastrointestinal	0/5	2/10	2/9
• Pulmonary	1/5	1/9	2/6
• Breast	0/8	1/7	1/3
• Hematopoietic/Lymphoma	1/8	0/9	1/9
• Other	1/6	2/7	1/5