COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

75yo man with PMH of CAD presents with 2 months of expanding abdominal mass, 25lb weight loss and fatigue with exam notable for a large RUQ/epigastric protuberance. Patient was found to have AFP of 20 and MRI read consistent with hepatocellular carcinoma with multifocal hepatic lesions and a thrombus within the left portal vein. Then EGD revealed a prepyloric tumor and gastric varices. Now concerning for primary gastric carcinoma with liver metastases vs. two primary cancers. Liver biopsy was performed and results remain pending.

Clinical Question: What is the management of venous thromboembolism in cancer patients?

Background:

Pathophysiology

-Cancer is a prothrombotic state- mechanism is not entirely understood

1. Tissue factor (TF)= a transmembrane glycoprotein
   - the prime physiological initiator of coagulation
   - expressed in a variety of human cancers
   - induced by activation of oncogenes or inactivation of tumor suppressor genes
   - Overexpression of TF in tumor cells or elevated TF levels in association with microparticles in the systemic circulation may contribute to systemic hypercoagulability.
2. Carcinoma mucins, tumor hypoxia, inflammatory cytokines less evidence
3. Chemotherapy- can induce TF in tumor cells, downregulate protein C & S, damage vascular endothelium, platelet activation→activation of hemostasis

Risk factors

-type of cancer, advanced stage, initial period after diagnosis, hospitalization, major surgery, etc

Epidemiology

-greater than 1% of cancer pts per year. Up to 7x more likely than normal population to get VTE

-20% of deaths from VTE occur in cancer pts

Search Strategy

Database: PubMed

Search terms: "management of venous thromboembolism in malignancy", "randomized trials for treatment of venous thromboembolism in malignancy", "management of portal venous thrombosis in malignancy"

Klerk CP. The Effect of Low Molecular Weight Heparin on Survival in Patients With Advanced Malignancy. Journal of clinical oncology. 2005-02;23:2130-2135.

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened.	Patients with metastasized or locally advanced solid tumors. -physician's assessment of life expectancy was recorded prior to random assignment (<6 vs. ≥6months)	?
Inclusion criteria	Histologically documented solid malignant tumors that could not be treated curatively	?
Exclusion criteria	Life expectancy< 1month, pt had indication for AC (mechanical heart valves, previous venous thromboembolism, or atrial fibrillation), or had contraindication to LMWH, pregnant or would receive radiotherapy or chemotherapy leading to thrombocytopenia <50K platelets	?
Treatment group	14days of treatment with nadroparin subQ BID then 4 weeks nadroparin daily	148
No treatment group	14 days of placebo subQ BID then 4 weeks of placebo daily	154

*Nadroparin: antifactor Xa

Primary endpoints: Death as a result of any cause

Secondary endpoints:
-Major bleeding: clinically overt episodes that were associated with a decrease in Hb>2 g/dL, that led to transfusion of 2 or more units of bloods, or that were located retroperitoneal or intracranially
-Clinically relevant nonmajor bleeding: overt bleeding episodes that did not meet criteria above but led to medical intervention

- **Are the Results of the Trial Valid?**
  - Randomized: Yes, numbered boxes of syringes using a central computer generated #
  - All patients accounted for at end: No pts lost to follow-up, however 40 pts in nadroparin group and 32 pts in the placebo group d/c'd prior to completion of treatment

Table 3. Discontinuation Study Drug and Treatment Details

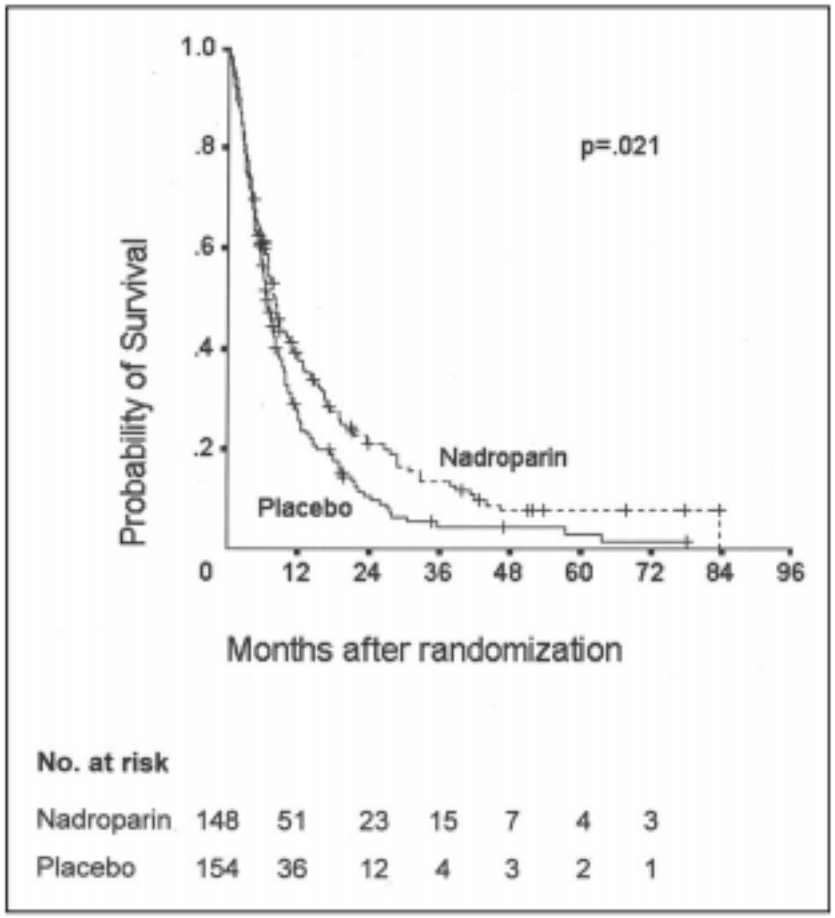
Characteristic	Nadroparin (n = 148) No. of Patients	%	Placebo (n = 154) No. of Patients	%
Patients who discontinued study medication before 6 weeks	40	27	32	21
Death	6	4	15	10
Withdrawal of treatment consent	17	11	8	5
Major bleeding	5	3	1	1
Clinically relevant nonmajor bleeding	5	3	0	0
Venous thromboembolism	2	1	3	2
Allergic reaction	0	0	1	1
Other	5	3	4	3
Concomitant antineoplastic treatment	92	62	90	58
Chemotherapy	37	25	53	34
Radiotherapy	48	32	28	18
Hormonal therapy	21	14	20	13
Other antineoplastic therapy	4	3	5	3

- Intention to treat: Yes; there was no crossover reported
- Blinding: Yes, the study was double-blinded to both investigators and patients
- Groups similar at start of trial: Most of the baseline characteristics were the same except:
  - Nadroparin had more breast ca. pts (31 vs. 19)
  - Nadroparin had fewer colorectal ca. pts (18 vs. 35)
- Equal treatment of groups? Yes, both sets of pts received the same instructions and were monitored on two occasions performing self-injection or injection by nurses.
- Did randomization work? Yes

- **Are the Results of the Trial important?**
  - Size of treatment effect: significant but minimal difference in primary outcome
  - Precision of the estimate of the effect: sample size is quite small, especially taking into account pts that did not complete the study, therefore the estimate of the effect is likely not too precise.

Endpoint	**Result** **N n=148** **P n-154**	**Significance**	**ARR**	**NNT**
Death prior to 6 weeks	N: 6 P: 15	--	--	--
Median Survival	N: 8.0mo P:6.6 mo	P=0.021	-10%	10
12 month survival	N: 51 P: 36	--	--	--
Morbidity	**Result**	**Significance**	**ARI**	**NNH**
Major Bleeding	N: 5 P:1	P=0.12	--	--
Clinically relevant bleeding	N: 7% P:1%	P=0.005	--	--

**N=nadroparin, P=placebo



- **Can I apply these results to my patient?**
  - Comparison of my patient to trial patients: My patient is similar to study patients in terms of age, advanced stage of solid tumor with metastases. He would NOT have qualified for this trial

given known portal venous thrombosis. Unfortunately, PVT in malignancy is not well studied, and there are no specific guidelines for treatment. In this patient, treatment is particularly complicated as with PVTs, one must weigh the risks of variceal bleeding, particularly gastric and splenic varices in this case vs. infarction of mesentery or embolism.

- All clinically important outcomes considered: This study demonstrates modest but significant differences in median survival at every time point. LMWH's beneficial effect remained long after administration of the drug, suggesting survival is unlikely due to prevention of pulmonary embolism, but rather LMWH plays a role in slowing cancer progression. Along with a handful of other randomized trials, this adds to a growing body of literature suggesting low molecular weight heparin is superior to both placebo and warfarin in prevention/treatment of venous thromboembolism.
- Likely benefits outweigh potential harms and cost: NO
    - +Does demonstrate modest improvement in survival
    - -Relatively low incidence of bleeding
    - -Discomfort of daily injections should not be minimized in end of life patients.
    - -Cost of nadroparin

References:
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2. Lee AY. Randomized Comparison of Low Molecular Weight Heparin and Coumarin Derivatives on the Survival of Patients With Cancer and Venous Thromboembolism. Journal of clinical oncology. 2005-02;23:2123-2129.
3. Klerk CP. The Effect of Low Molecular Weight Heparin on Survival in Patients With Advanced Malignancy. Journal of clinical oncology. 2005-02;23:2130-2135.
4. Wolberg AS. Venous Thromboembolism: Risk Factors, Biomarkers, and Treatment. Arteriosclerosis, thrombosis, and vascular biology. 2009-03;29:296-297.
5. Meyer G. Comparison of Low-Molecular-Weight Heparin and Warfarin for the Secondary Prevention of Venous Thromboembolism in Patients With Cancer<subtitle>A Randomized Controlled Study</subtitle>. Archives of internal medicine (1960). 2002-08;162:1729.
6. Haas S. Heparin based prophylaxis to prevent venous thromboembolic events and death in patients with cancer - a subgroup analysis of CERTIFY. BMC cancer. 2011;11:316.
7. Sogaard KK. Portal vein thrombosis; risk factors, clinical presentation and treatment. BMC gastroenterology. 2007;7:34.
8. Lyman GH. American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer. Journal of clinical oncology. 2007-12;25:5490-5505.