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Tromboembolismo venoso (TEV) e cancro: se, quando e come passare da trattamento iniziale e di breve termine a quello di lungo termine

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Standard treatment of VTE with Vitamin K antagonists (VKA)

Initial treatment:
LMWH therapeutic dose + within 24 hours start VKA
Continue both drugs for 5-7 days, until INR ≥ 2 (for 2 consecutive days)

↓

Long-term treatment:
When INR ≥ 2 stop LMWH
Continue VKA for 3-6 months

↓

Indefinite treatment:
In case of recurrent VTE, continue VTE indefinitely

Issues in VTE treatment in the Cancer Patient

- High rate of recurrences
- High rate of bleeding with anticoagulant therapy
- Problems with VKA anticoagulation during surgery, invasive procedures (i.e. biopsies), and chemotherapy

Standard treatment of VTE in cancer with LMWH

Initial treatment:
LMWH therapeutic dose (200 U.I./Kg/d)
Continue for 1 month

Long-term treatment:
Reduce LMWH to 75% of the initial dose
Continue LMWH for 3-6 months

Indefinite treatment:
In case of "active" cancer, or during chemotherapy
Continue with LMWH? VKA? …

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014

Gary H. Lyman, Kari Bohlke, Alok A. Khorana, Nicole M. Kuderer, Agnes Y. Lee, Juan Ignacio Arcelus, Edward P. Balaban, Jeffrey M. Clarke, Christopher R. Flowers, Charles W. Francis, Leigh E. Gates, Ajay K. Kakkar, Nigel S. Key, Mark N. Levine, Howard A. Liebman, Margaret A. Tempero, Sandra L. Wong, Mark R. Somerfield, and Anna Falanga

J Clin Oncol 33. © 2015

LMWH is recommended for the initial 5 to 10 days of treatment of established VTE as well as for long-term secondary prophylaxis for at least 6 months.

Long Term Treatment

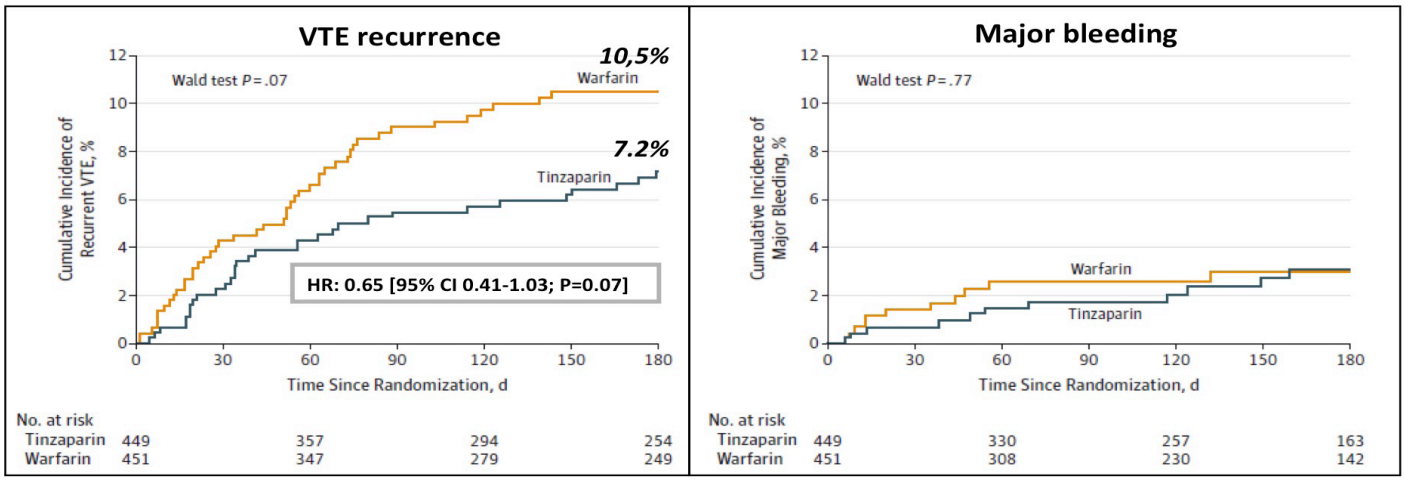
According to the results of three randomized clinical trials,

LMWHs have the potential to provide a more effective antithrombotic regimen in cancer patients with VTE than the conventional treatment

and are not associated with an increased hemorrhagic risk

(Lee et al. 2003; Meyer et al. 2002; Hull et al. 2006)

CATCH study: Results



The study showed a trend towards a superior efficacy with the LMWH compared to VKA in reducing the relative risk of VTE recurrence and all bleeding thus confirming the value of LMWH therapy in patients with CAT.

A.Y.Y. Lee et al. JAMA

Cochrane metanalysis

Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer (Review)

This metanalysis included randomized controlled trials (RCTs) comparing long-term treatment with LMWH versus oral anticoagulants (VKA or ximelagatran) in patients with cancer and symptomatic objectively confirmed VTE.

Objectives:

- To compare the efficacy and safety of LMWH and oral anticoagulants for the long-term treatment of VTE in patients with cancer.

E.A. Akl et al. Cochrane Database of Systematic Reviews 2014

Cochrane metanalysis
Results

- *For the long-term treatment of VTE in patients with cancer, **LMWH** compared with VKA **provided no statistically significant survival benefit** but a **statistically and patient important reduction in VTE**.*

- *The findings did not exclude a beneficial or harmful effect of LMWH compared with VKA in terms of bleeding outcomes or thrombocytopenia.*

E.A. Akl et al. Cochrane Database of Systematic Reviews 2014

Association between anticoagulant treatment duration and risk of venous thromboembolism recurrence and bleeding in clinical practice

- Studio retrospettivo osservazionale per valutare se la durata della terapia anticoagulante variava in base al rischio di recidive di TEV e al rischio emorragico.

- Pazienti con TEV patients che assumevano per la prima volta la terapia anticoagulante sono stati identificati dall'HealthCore Integrated Research Database tra il 2007 e il 2011 e divisi in tre categorie di TEV: 'provoked', '**cancer-related'**, and 'unprovoked'.

- E' stata valutata l'associazione fra la durata della terapia anticoagulante e le categorie di rischio per TEV e per emorragie nel mondo reale.

Kaatz. et al. Thromb Research 2014

Results

- I pazienti con TEV 'provoked' o 'cancer-related' avevano una durata del trattamento significativamente inferiore a quelli con TEV 'unprovoked',
- Nessuna differenza invece appariva fra i pazienti con TEV 'cancer-related' e 'provoked'.
- Quindi anche se l'8th ACCP guidelines raccomandava che I pazienti con TEV 'cancer-related' dovevano continuare la terapia fino a quando il cancro è attivo, in questo studio I pazienti con TEV 'cancer-related' non avevano un trattamento deverso da quell con TEV 'provoked'.

Kaatz. et al. Thromb Research 2014

Guidelines: Treatment CAT

- International academic institutions consider low-molecular-weight heparins (LMWH) as the preferred option for the treatment of cancer-associated VTE

	Long-term treatment	Treatment duration
AIOM (*Italian association of medical oncology)*	LMWH	3 to 6 months then LMWH **until cancer resolution**
NCCN (*US national Comprehensive Cancer Network)*	LMWH or VKA	3 to 6 months for DVT; 6 to 12 month for PE
ASCO (*American Society of Clinical Oncology)*	LMWH	At least 6 months
INCa (*Institut National du Cancer)* and International	LMWH	3 to 6 months then VKA or LMWH **until cancer resolution**
ACCP (*American College of Chest Physicians)*	LMWH	3 to 6 months then VKA or LMWH **until cancer resolution**

Cancro e TEV

Durata della Terapia Anticoagulante

- Al termine del trattamento anticoagulante, i pazienti neoplastici con TEV presentano un rischio di recidive che è circa il doppio rispetto ai pazienti non neoplastici (Prandoni et al. 1996; Hansson et al. 2000; Heit et al. 2000).
- I quesiti aperti sono:
  - Come identificare i pazienti in cui continuare il trattamento a tempo indefinito
  - Quale trattamento (LMWH o AVK) è più efficace

Cancro e TEV

Durata della Terapia Anticoagulante Fattori predittivi

- Sono stati ricercati fattori predittivi che potessero aiutare il medico a decidere sulla durata della terapia nel singolo paziente:
- Fra i fattori associati ad un aumentato rischio di TEV dopo la sospensione dell'anticoagulazione vi sono:
  - Il trombo venoso residuo, valutato con ultrasonografia a compressione
  - Alterazioni del D-dimero, misurato il giorno della sospensione and poi 1 mese dopo.

The role of D-dimer and residual vein obstruction (RVO) in recurrence of VTE after anticoagulation withdrawal in cancer patients

- The predictive value of D-dimer and RVO, alone or in combination, for VTE over a 2-year follow-up in a cohort of 88 cancer patients after oral anticoagulant therapy withdrawal following a first episode of proximal DVT of the lower limbs.

Table 2. Recurrence rate for VTE according to the combination of D-d and RVO at T1 and T2 after OAT withdrawal.

	Normal D-d without RVO	*Normal D-d with RVO*	*Abnormal D-d without RVO*	*Abnormal D-d with RVO*
D-d and RVO at T1				
Recurrence rate% (95% CI) n./total	12 (3-31)° 3/25	23 (10-40) 8/35	14.3 (0-58) 1/7	58.3 (28-85) 7/12
% patient-years (95% CI) n./years	7.3 (2-20)@ 3/41	17.4 (8-31) 8/46	10 (0-44) 1/10	41.1 (18-67) 7/17
D-d at T2 and RVO at T1*				
Recurrence rate% (95% CI) n./total	0.0 (0-19)# 0/17	23.1 (9-44) 6/26	26.6 (8-55) 4/15	42.8 (22-66)^ 9/21
% patient-years (95% CI) n./years	0.0 (0-12)## 0/28	15.8 (6-31) 6/38	17.4 (5-39) 4/23	36 (18-57)^ 9/25

**No recurrences were observed between T1 and T2; °p=0.005 vs abnormal D-d with RVO; @p= 0.0044 vs. abnormal D-d with RVO; # and ## p=0.0002 vs. abnormal D-d with RVO; ^Hazard ratio for recurrence= 12.25 (95% CI: 1.5-100.3; p=0.02), after adjustment for age and sex, vs. normal D-d without RVO.*

RVO, determined by compression ultrasonography on the day of OAT suspension (T1), **and abnormal D-d** (*cut-off value: 500 ng/mL*), measured at T1 and 30±10 days afterwards, **are independent risk factors** for **recurrent VTE** in **cancer patients**.

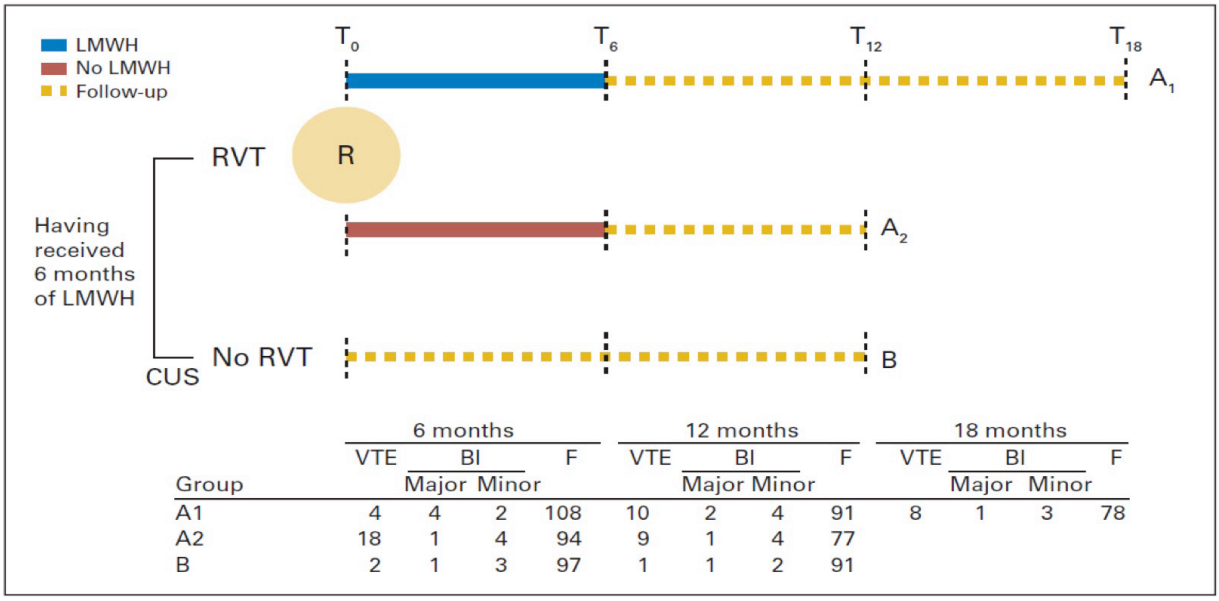
B. Cosmi et al. Haematologica 2005

Optimal Duration of Low Molecular Weight Heparin for the Treatment of Cancer-Related Deep Vein Thrombosis: The Cancer-DACUS Study

- **Purpose:** to evaluate the role of residual vein thrombosis (RVT) to assess the optimal duration of anticoagulants in patients with cancer who have DVT of the lower limbs.
- Patients with active cancer and a first episode of DVT treated with LMWH for 6 months were enrolled.
- Patients with RVT were randomly assigned to:
  - continue (**group A1**) or
  - discontinue (**group A2**) LMWH for an additional 6 months;
  - Patients without RVT stopped LMWH (**group B**).
- The primary end point was recurrent venous thromboembolism (VTE) during the 1 year after discontinuation of LMWH, and the secondary end point was major bleeding.

M. Napolitano et al. JCO 2014

Study design



	6 months				12 months				18 months			
	VTE	BI		F	VTE	BI		F	VTE	BI		F
Group		Major	Minor			Major	Minor			Major	Minor	
A1	4	4	2	108	10	2	4	91	8	1	3	78
A2	18	1	4	94	9	1	4	77				
B	2	1	3	97	1	1	2	91				

M. Napolitano et al. JCO 2014

Results

Table 3. Recurrent Thromboembolic and Bleeding Events by Treatment Group and Cancer Site

Event	Group A1 (n = 119) No.	%	Group A2 (n = 123) No.	%	Group B (n = 105) No.	%	P*
Overall events†	22/119	18.5	27/123	21.9	3/105	2.8	< .001
Isolated DVT	9/18	50	19/27	70.4	2/3	66.7	.379
DVT and PE	7/18	38.9	7/27	25.9	0		.333
PE only	2/18	11.1	1/27	3.7	1/3	33.3	.183
DVT in not previously affected leg	4/18	22.2	7/27	25.9	1/3	33.3	.906
Major bleeding†	7	5.8	2	1.6	2	1.9	.109
Minor bleeding†	9	7.6	8	6.5	5	4.8	.689
Death (as a result of cancer progression)	12	10.1	19	15.4	11	10.5	.366

NOTE. Group A1, patients with residual vein thrombosis (RVT) who continued low-molecular-weight heparin (LMWH) for an additional 6 months; group A2, patients with RVT randomly assigned to stop LMWH; group B, patients without RVT who stopped LMWH. No. columns indicate No. of overall events per total patient group.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

*Bonferroni-adjusted *P* values refer to χ^2 test.

†Events after discontinuation of LMWH: VTE, 18; major bleeds, 3; minor bleeds, 7.

All patients underwent RVT assessment after 6 months of LMWH.

In those with residual RVT who stopped LMWH (group A2), the incidence of subsequent recurrent VTE was 21.7% compared with 2.8% in patients without RVT who stopped treatment (B), an almost eight-fold increased risk.

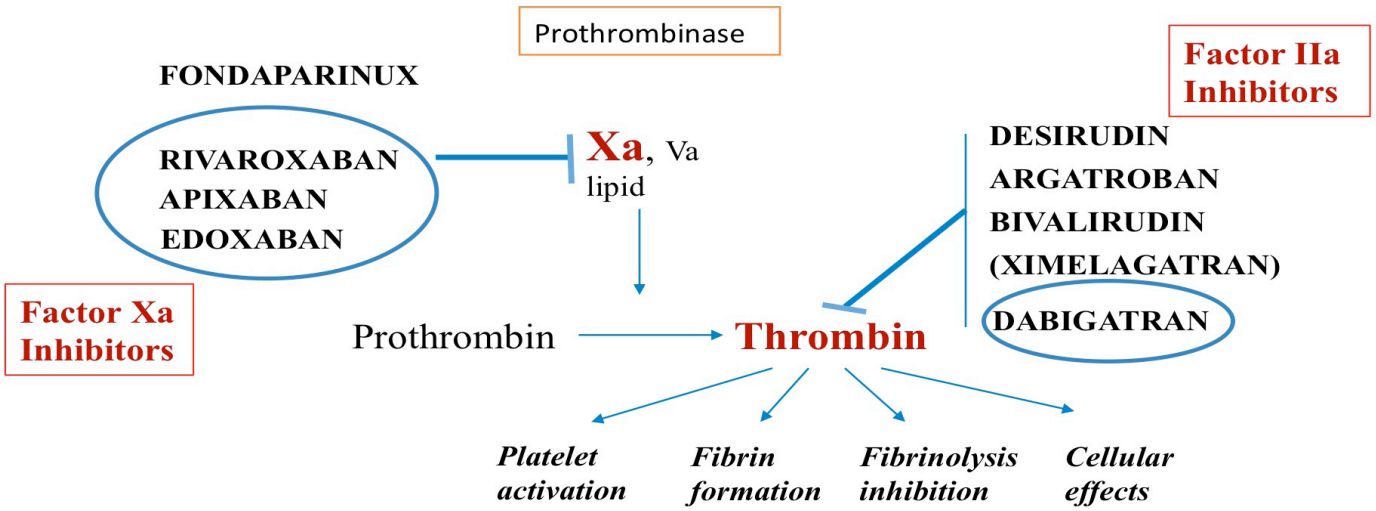
M. Napolitano et al. JCO 2014

Conclusion

- The results indicate that, after 6 months of standard treatment with LMWH for DVT, **the absence of RVT identifies patients with cancer at a low risk for recurrent thrombotic events.**
- This possibility is important in driving a management strategy for both prevention of recurrences and selection of patients who may benefit from a short period of anticoagulation.

M. Napolitano et al. JCO 2014

Direct Oral Anticoagulants (DOACs)



DOAC in Patients with Cancer

- The new oral anticoagulants offer an attractive option because of their oral administration, fixed-dose, and lack of routine laboratory monitoring.
- The results of phase III trials of DOACs vs Warfarin for VTE treatment support the efficacy and safety of DOACs in the management of VTE in the general population.
- However, generalizing these findings to cancer patients with VTE is difficult since very few cancer patients were included in those trials.
- Finally, in the cancer setting, their role in comparison with the current standard of care, i.e. LMWH, is still unclear.

Comments: DOACs in Treatment of CAT

Data come from:

- underpowered subgroup analyses in selected patients
- study population of "cancer" or "active cancer" not clearly defined and inconsistent among DOAC trials
- no details regarding prognostic factors (e.g., cancer types, treatment, stages) and no data on death
- TTR not reported for control groups
- duration of treatment and follow-up unknown
- "cancer" patients in DOAC trials are different from those in LMWH trials

Patients with cancer have multiple factors to consider:

- They are at high risk for hemorrhage for reasons including chemotherapy-induced **thrombocytopenia** or receipt of **antiangiogenic** therapy.
- DOAC may have a potential limitation in cancer patients who suffer abnormal liver function and severe **renal impairment** or have **poor attitude to oral intake**.
- DOAC may cause **drug interactions** with chemotherapeutic agents, which may result in less efficacy and higher bleeding than that observed in patients without cancer

Drug interactions

- Strong and moderate modulators of the CYP3A4 enzyme, especially those that also interact with P-glycoprotein, carry the highest relative risk for significant drug interactions with the DOACs.
- Two strong inhibitors of CYP3A4 were identified: **1. enzalutamide**, an androgen receptor antagonist used to treat castration-resistant prostate cancer, and **2. dexamethasone**, a glucocorticoid used for its antitumor effects in many lymphoid malignancies and for the treatment and palliation of various cancer-related complications, including nausea and vomiting.
- Use of these drugs in combination with any of the three DOACs could result in increased plasma concentrations of the DOAC.

J.M. Connors. The Oncologist 2014

International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer

- **Early maintenance (10 days to 3 months) and long-term (beyond 3 months):**
- LMWH should be used for a minimum of 3 months to treat established VTE in patients with cancer (grade 1A).
- **After 3–6 months, termination or continuation of anticoagulation** (LMWH, VKA, or direct oral anticoagulants) should be based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance, in the absence of data).

Farge et al. Clinical Oncol 2016

ACCP Guidelines Antithrombotic Therapy for VTE Disease

- In patients with DVT of the leg or PE and **active cancer** ("cancer-associated thrombosis") and
  - ❖ who do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B),
  - ❖ or have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).
- Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

Kearon et al. Chest 2016

Patient's risk of bleeding

- For the decision about whether to stop treatment at 3 months or to treat indefinitely ("extended treatment"), categorize a patient's risk of bleeding on anticoagulant therapy as:
  - **Low**: no bleeding risk factors; 0.8% annualized risk of major bleeding
  - **Moderate**: one bleeding risk factor; 1.6% annualized risk of major bleeding
  - **High**: two or more bleeding risk factors; 6.5% annualized risk of major bleeding.

Kearon et al. Chest 2016

Linee Guida AIOM 2016

- La durata dell'anticoagulazione va prolungata almeno per tutto il tempo in cui il cancro è in fase attiva o vi sono terapie antitumorali in corso, a meno che non sussistano controindicazioni **(Livello di evidenza 4).**
- Il ruolo del trombo residuo valutato mediante metodica ultrasonografica è argomento di ricerca.
- Pertanto, la presenza o l'assenza del trombo residuo dopo 6 mesi di terapia anticoagulante standard con EBPM non dovrebbe influenzare la decisione clinica relativamente alla durata della terapia anticoagulante.

Edizione 2016

ASCO 2013

Treatment Beyond 6 Months

- No published studies address optimal anticoagulation beyond the first 6 months in patients with cancer.
- However, it is the consensus of the Panel, based on extrapolation from patients with idiopathic VTE, that continuing anticoagulation beyond 6 months should be considered for selected patients because of the persistent high risk of recurrence in those with active cancer.
- The decision to continue anticoagulation must be balanced against the risk of bleeding, cost of therapy, quality of life, life expectancy, and patient preference.

Lyman et al. JCO 2013

Treatment of venous thromboembolism in patients with cancer: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET)

- In patients with malignancies, the long-term prophylaxis against VTE should be continued while the cancer is "active" and/or the patient is undergoing antitumoral treatment (grade D).

Imberti, et al. Thrombosis Research 2009

M.P.

- Paziente maschio di 72 anni
- Gennaio 2013: è sottoposto a biopsia vescicale (carcinoma uroteliale)
- Aprile 2013 esegue cistectomia radicale + linfoadenectomia dei linfonodi iliaci + confezionamento di neovescica ileale ortotopica.
- Maggio/Giugno 2013: inizia programma di chemioterapia; dopo una sola dose di cisplatino, Embolia polmonare dx con infarto polmonare (ECD venoso AAII: negativo).
- Viene sospesa la CT ed esegue solo Radioterapia dei linfonodi
- Per l'EP inizia Clexane 8000 UI x 2/die (peso: 96 kg) per 1 mese, poi riduce a 6000 UI x 2/die fino a Dicembre 2013, quando passa a Clexane 4000 UI die.

- A Febbraio 2014, dopo 8 mesi di t. anticoagulante con LMWH, esegue rivalutazione:
  - TAC torace negativa
  - Visita oncologica: non evidenza di malattia, prosegue con follow up oncologico
- Il medico decide di sospendere Clexane.

- A Luglio 2015, ad una TAC di controllo, riscontro di formazioni linfonodali di aspetto patologico localizzati in sede para-aortica sx, per cui esegue radioterapia (che si conclude a Dic. 2015).
- A dicembre 2016 per dolore all'arto inferiore destro si reca in Pronto Soccorso. All'ECD venoso: trombosi completa della vena poplitea dx
- Ricomincia Clexane 8000 UI x 2/die