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Considerations on the use of low molecular weight heparins in patients with cancer and chronic kidney disease

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Chronic kidney disease (CKD) is frequent among patients with cancer. For instance, according to the Belgian Renal Insufficiency and Anticancer Medications (BIRMA) study, 64% patients with cancer had a glomerular filtration rate (GFR) <90 ml/min per 1.73m2 and 16% of them presented with a mildly to severely decreased GFR (i.e. <60ml/min per 1.73m2).[1] A similar prevalence of CKD among cancer patients was observed in the French IRMA-1 and -2 studies with nearly 12% of cancer patients having a GFR <60 ml/min.[2,3] From this point of view, and because thromboprophylaxis is required for most hospitalised patients with active (or clinical suspicion of) cancer without contraindication to such therapy, selection of the most appropriate prophylactic anticoagulant therapy for CKD patients with cancer remains important.

In most patients with cancer, LMWHs are the preferred prophylactic anticoagulant therapy (*see consensus*). For instance, their advantages against subcutaneous unfractionated heparin (UFH) are numerous (e.g. once-daily administration, better pharmacokinetic profile, decreased risk of heparin-induced thrombocytopenia). Therefore, LMWHs are recommended for the initial 5-10 days of treatment after VTE as well as for the long-term (six months) secondary prophylaxis of venous thromboembolism (VTE). However, the safe use of LMWHs implies a preserved renal function (i.e. GFR >50 ml/min). In patients with lower GFR (30-50 ml/min), LMWHs remain the first choice but bioaccumulation can already occur and daily doses should be adapted according to the manufacturer's recommendations. For example, enoxaparin needs to be reduced (30 mg/day subcutaneously for venous thromboembolism (VTE) prophylaxis). The most important risk of bleeding concerns patients with severe renal impairment (GFR <30 ml/min) and LMWHs are no more recommended. However, some data suggest that particular LMWHs (i.e. dalteparin, tinzaparin) do not accumulate on a short period at prophylactic dose even in case of severe CKD. By inference, it was suggested that LMWHs with little or no bioaccumulation (e.g. dalteparin, tinzaparin) should be preferred in patients with severe CKD.[4] In case of severe CKD, unfractionated heparin (UFH) (e.g. 5000 U 2-3 times/day) can be an option for thromboprophylaxis in hospitalised patients with cancer. Indeed, the liver is a main site of heparin biotransformation thereby limiting the risk of bleeding. In order to limit the bleeding risk in patients with cancer and risk factors such as moderate to severe CKD (i.e. GFR <60 ml/min per 1.73m2), many experts and guidelines propose to monitor the anticoagulant effects of LMWHs by measurement of the ability of plasma to inhibit factor Xa. Patients with renal impairment are potentially at risk of bleeding because of reduced LMWHs clearance and subsequent prolonged anticoagulants effect.[5] In one study, an interesting strong linear relationship was demonstrated between creatinine clearance, enoxaparin clearance (r=0.85; P=0.001) and

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the anti-factor Xa level (P<0.0005).[6] This observation has been confirmed in meta-analysis with enoxaparin.[7] In addition, a (non-cancer specific) study showed that factor Xa did not accumulate significantly for tinzaparin, but did for enoxaparin (prophylactic doses) in elderly patients with low GFR.[8] However, even if this monitoring (peak and through) has been recommended for patients with severe renal impairment (<30 ml/min), only limited data are available on the use of factor Xa inhibition to monitor and adjust LMWH.[9] Accordingly, the anti-factor Xa remains of limited value in CKD patients because it is poorly correlated with bleeding, especially in patients with a high risk for bleeding complications.[10] Also, the factor Xa assay remains expensive and is not routinely performed. Moreover, it is not refunded by the RIZIV/INAMI. Finally, it is interesting to note that potential other monitoring tools exist for the monitoring of LMWH including thrombin generation time (TGT), platelet contractile force (PCF) and clot elastic modulus (CEM). For instance, TGT of end-stage renal disease patients supported a 50% greater anticoagulation for a similar level of anti-Xa activity (i.e. 0.5-3.0 IU/ml).[10]

Older age and CKD are in close relation as prevalence of CKD significantly increases with age. However, data about renal function of elderly patients with cancer are highly limited. Elderly patients often present a number of factors that may significantly increase the risk of bleeding in comparison to younger patients. These factors include other comorbid medical conditions, CKD, polypharmacy, risk of falls and dementia. Accordingly, the clinician should consider these factors before prescribing anticoagulation therapy. Also, clinicians should be aware that GFR equations may be limited in elderly patients. For instance, Schaeffner *et al*. have recently reported that the most common GFR equations such as MDRD or CKD-EPI considerably overestimate the real GFR (up to 30-40%) in patients aged 70 years or older.[11] Therefore, the risk of accumulation could be important in elderly patients with estimated GFR <40-45 ml/min as true GFR can be <30 ml/min. The clinicians should be aware of these limitations before prescribing LMWHs in elderly cancer patients.

The standard initial treatment of VTE or thrombosis in patients with active malignancy is LMWH for a minimum duration of 3 months (ideally at least 6 months) in patients with GFR >50 ml/min/1.73m2. LMWHs are preferred for the acute management of VTE in cancer patients because they do not require hospitalisation or monitoring, and are the preferred option for long-term therapy (*see consensus*). Again, the risk of LMWH bioaccumulation appears to be greatest in patients with a GFR <30 ml/min and the use of therapeutic LMWH doses and uncertainty remains in patients with a GFR between 30 and 50 ml/min. The use of enoxaparin is associated with specific dosing recommendations in these situations. The manufacturer recommends 1 mg/kg/d s.c. for VTE treatment (and 30 mg s.c. daily for VTE prophylaxis; see above) in patients with GFR <30 ml/min. It is important to note that there is an increased risk of bleeding if standard, unadjusted doses are used in patients with a GFR <30 ml/min.[7] Of interest, it was demonstrated that the clearance of enoxaparin was reduced by 31% and 44% in patients with a GFR of 30-60 ml/min and <30 ml/min, respectively.[12] This observation paves the way to reduce enoxaparin daily dose if the GFR is <50 ml/min or even <60 ml/min.[13] Few data on dalteparin suggest that no bioaccumulation occurs after a median seven days of prophylactic dose dalteparin. Finally, warfarin is the option for long-term treatment of VTE in cancer patients (*see consensus*). Warfarin can be safely administered to CKD patients, keeping in mind that CKD patients always exhibit higher bleeding risk than non-CKD patients.

Cancer patients with established VTE who undergo haemodialysis are belonging to a particular population. It is to note that randomised controlled trials have evaluated LMWH for preventing thrombosis of the dialysis circuit, and LMWH has been approved for this indication in many countries. However, the use of LMWH for daily administration (e.g. daily dialysis, VTE treatment) can lead to significant bioaccumulation, and hence dose adjustments may be necessary. Importantly, LMWH is not removed from the plasma during haemodialysis/filtration and the anti-factor Xa activity in the plasma remains relatively stable even if a minor elimination of the LMWH may occur with high-permeability membranes. The data to suggest LMWHs in patients with established VTE undergoing haemodialysis are insufficient. Clinical trials using dalteparin or tinzaparin in patients undergoing haemodialysis are ongoing but data suggest that these LMWHs can bioaccumulate in such patients.[14] Therefore, the use of such therapy in contraindicated in that population.

In conclusions, most recommendations are to limit or avoid the use of LMWHs in patients with moderate to severe CKD. In all situations, the clinicians should follow the manufacturer's specifications and should consider the patient's characteristics that can influence the determination of the LMWHs daily dose.

References

1. Janus N, Launay-Vacher V, Byloos E, et al. Cancer and renal insufficiency results of the BIRMA study. Br J Cancer. 2010;103(12):1815-21.

2. Launay-Vacher V, Oudard S, Janus N, et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer. 2007;110(6):1376-84.

3. N. Janus, S. Oudard, P. Beuzeboc, J, et al. Prevalence of renal insufficiency in cancer patients: Data from the IRMA-2 study. J Clin Oncol. 27:15s, 2009 (suppl; abstr 9559).

4. Di Nisio M, Carrier M, Lyman G, et al. Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12(10):1746-9.

5. Lai S, Coppola B. Use of enoxaparin in end-stage renal disease. Kidney Int. 2013;84(3):433-6.

6. Backer R, Spencer F, Gibson M, et al. Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. Am Heart J. 2002;143(5):753-9.

7. Lim W, Dentali F, Eikelboom J, et al. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. Ann Intern Med. 2006;144(9):673-84.

8. Mahe I, Gouin-Thibault I, Drouet L, et al. Elderly medical patients treated with prophylactic dosages of enoxaparin: influence of renal function on anti-Xa activity level. Drugs Aging. 2007;24(1):63-71.

9. Nutescu E, Spinler S, Wittkowsky A, et al. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009; 43(6):1064-83.

10. Brophy D, Martin E, Gehr T, et al. Enhanced anticoagulant activity of enoxaparin in patients with ESRD as measured by thrombin generation time. Am J Kidney Dis. 2004;44(2):270-7.

11. Schaeffner E, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med. 2012;157(7):471-81.

12. Hulot J, Montalescot G, Lechat P, et al. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. Clin Pharmacol Ther. 2005;77(6):542-52.

13. Kruse M, Lee J. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. Am Heart J. 2004;148(4):582-9.

14. Easaw J, Shea-Budgell M, Wu C, et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment. Curr Oncol. 2015;22(2):144-55.