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RECURRENT PULMONARY EMBOLISM IN METASTATIC BREAST CANCER: RESPONDING TO A DOSE REDUCTION OF ANTICANCER TREATMENT

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RECURRENT PULMONARY EMBOLISM IN METASTATIC BREAST CANCER: RESPONDING TO A DOSE REDUCTION OF ANTICANCER TREATMENT

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Abstract

Venous thromboembolism (VTE) is a major complication in cancer patients despite anticoagulation. In fact this is the second cause of death in them, only behind the malignancy itself. Therefore, optimal treatment is crucial.

Low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) have been included as therapeutic options based on clinical trials.

But the issue here is that there are other contributing factors to the VTE apart from the cancer, such as the anticancer treatment. In fact, the recent incorporation of CDK4/6 inhibitors, such as Palbociclib, has shown to increase these episodes. Â

We present a case of multiple recurrences of VTE despite anticoagulation, which only responded after a reduction in the dose of Palbociclib.

This should change cliniciansâ€™ perspective at the time of treating recurrent VTEs in this population and think promptly about a dose reduction of the anticancer treatment if known to be associated to VTE. Â

Background

Patients with cancer have an elevated risk of acute and recurrent venous thromboembolism (VTE) despite anticoagulation. This issue poses a challenge to clinicians as there is not good evidence to suggest the best practice in this situation[1].

For many years, low-molecular weight heparin (LMWH) has been considered an optimal anticoagulant for cancer-related VTE, and more recent data have concluded that direct oral anticoagulants (DOACs) are also good alternatives[2].

As such, in the event of recurrent VTE, the advice would include (based on retrospective studies) either escalating LMWH doses or switching from DOACs to LMWH[3].

We present here a case of recurrent/new VTEs on a patient with metastatic breast cancer despite optimal anticoagulation, who only responded to a reduction of her antineoplastic treatment

Case Report

A 73 -year?old female with a background of breast invasive ductal carcinoma, oestrogen receptors (ER) positive and Her-2 negative, presented with a several weeks history of lateral chest pain on the left side.

She was otherwise healthy and quite active.

She underwent a MRI of her chest to check the status of her breast prosthesis. This showed an expansile lytic lesion in the anterior aspect of her left third rib suspicious of malignancy.

A CT scan confirmed this lesion and showed multiple bilateral pulmonary emboli and numerous small mixed sclerotic and lytic axial skeletal lesions. A bone scan was also performed and reported multiple small thoracic vertebral metastases and a few smaller lumbar deposits with a patchy uptake throughout the ribs and a left posterior skull metastasis.

The patient had not reported any shortness of breath, although, when asked retrospectively, she mentioned that perhaps recently she had noticed more difficulties when going for long walks or upstairs.

A therapeutic dose of LMWH was started and although initially a biopsy was planned, then this was abandoned due to risks considerations.

The patient was started on a combination of Letrozole and Palbociclib.

She coped well with this treatment but struggled with the daily LMWH injections and after 8 weeks of treatment, this was switched to Rivaroxaban after a discussion with the Haematologists.Â

A CT scan repeated 3 months later to assess response showed stable bone metastases but persisting multilobar pulmonary emboli. On further questioning, the patient reported more shortness of breath on the previous weeks. Rivaroxaban was then

stopped and switched back toÂ

LMWH therapeutic dose. Her shortness of breath improved significantly but she started to struggle again with the daily injections after 6 weeks on them.

This time she was switched to Apixaban 5mg twice daily and a later CT repeated 3 months after, reported an unchanged chronic thrombus in the proximal right lower lobe pulmonary artery and stable bone metastases.

Around 4 months later, the patient contacted us complaining of new shortness of breath on moderate exertion. Her CT was brought forward and it showed stable bone metastases but new pulmonary emboli in the segmental arteries and sub-segmental vessels in the left lower lobe.

Her treatment was switched again to LMWH monitoring anti-Xa. After an initial benefit, another CT showed again new pulmonary emboli without any clinical impact this time.

On further discussion with Haematology, the dose of LMWH was increased by 20% and we decided to reduce the dose of Palbociclib from 125mg to 100mg.

The patient had never had any signs of deep venous thrombosis and she had always been very active.

After around 4 weeks of daily injections, she could not cope anymore. It was then decided to try back Rivaroxaban.

Another CT was repeated after being >2 months again on Rivaroxaban. This CT did not show any evidence of new pulmonary emboli and continued to report stable disease.

Currently, >2 years later, the patient continues well, without any further changes and since the reduction on Palbociclib, her repeated CTs show no evidence of further VTE. Â

Discussion

Cancer associated thrombosis is a highly prevalent and potentially lethal complication in patients with malignancies. It has been estimated that the annual incidence of VTE in cancer patients is 0.5% in comparison to 0.1% in the general population[4].

Moreover, VTE is the second most frequent cause of death from malignancy, second to cancer itself[5].

It presents some peculiarities that differentiate it from other VTE such as different risk factors, pathological mechanisms, difficulties in diagnosis and uncertainties about optimal treatment.

Although breast cancers are associated with low risk of VTE in relation to other types of cancer[6],

VTE is frequently detected anyway as breast cancer is one of the most prevalent neoplasias around the world.Â

Other risk factors contributing to VTE are the presence of metastatic disease, treatment with chemotherapy, mainly platinum or taxanes, tyrosine kinase inhibitors, immunomodulatory agents and more recently the cyclin dependent kinase (CDK) 4/6 inhibitors such as Palbociclib[6,7].

Our patient presented here, had metastatic disease involving the bones and an incidental pulmonary emboli at diagnosis.

She was started on therapeutic dose of LMWH and palliative treatment with Palbociclib and Letrozole as first line for her metastatic breast cancer.

Although VTE events were rarely reported following this CDK4/6 inhibitor within PALOMA-1 (Letrozole vs Palbociclib and Letrozole) and PALOMA-3 (Palbociclib and Fulvestrant or placebo) clinical trials, overall an incidence of around 1.2-2% was confirmed[8,9].

But this incidence seems to be low when compared to the real-world experience as reported by Watson *et al*. These authors confirmed an 11% incidence of VTE and they suggested that further research is needed to assess if a prophylactic anticoagulation should be considered for these patients[10].

Typically patients present with symptoms of shortness of breath, chest pain, tachypnea or rapid heart rate and authors from those trials concluded that patients should be monitored for any of these symptoms.

Unfortunately, these symptoms, as in our patient, may be subtle and not considered relevant or the patient may not even present with any symptoms at all, at least for a period of time.

This makes even harder a proper diagnosis. Â

Our patient showed several episodes of VTE recurrence which unfortunately this is frequent despite being on anticoagulation, and this still poses a challenge to clinicians as there is not[11,12] Â

a high-quality evidence to guide practice in this situation.

For many years LMWH has been the standard as it had demonstrated superiority over warfarin in reducing the risk of VTE in patients with cancer[13].

However, recently, the Hokusai VTE Cancer trial (Edoxaban for the Treatment of Cancer-Associated VTE)[14]randomised 1046 patients with cancer associated VTE to receive, after a minimum course of

5 days of LMWH, oral edoxaban or dalteparin 200 U/kg once daily for 1 month followed by 150 U/kg for at least 6 months and up to 12 months.

Edoxaban showed non inferiority in comparison to dalteparin and those patients also showed fewer episodes of VTE recurrence[15].

The SELECT-D (Comparison of an oral factor Xa inhibitor with LMWH in patients with cancer with VTE) trial randomised 406 patients to receive rivaroxaban 15mg twice daily for 3 weeks followed by 20mg once daily for 6 months or dalteparin 200 U/kg once daily for 1 month followed by 150 U/kg once daily for 2â€“6 months[16].

VTE recurrence rates were less frequent with rivaroxaban.Â

And the Caravaggio trial as well has shown non-inferiority of oral apixaban in comparison to dalteparin for the treatment of cancer-associated recurrent VTE[17].

In fact, the International Society of Thrombosis and Haemostasis (ISTH) has suggested the use of rivaroxaban or edoxaban for cancer associated thrombosis in patients with low risk of bleeding, but to consider LMWH[18]as an acceptable alternative for cancer patients with a higher risk of bleeding such as gastrointestinal cancers.

The NCCN guidelines recommend LMWH as the preferred option in patients with a pulmonary embolism and advanced metastatic cancer, although rivaroxaban and apixaban are also accepted as alternatives, especially for patients who do not cope well with daily injections[1].

Other recommendations have included changes between DOACs to LMWH or escalating LMWH doses by 20%-25% but these are based on limited retrospective studies[2,19].

What strikes us is the fact that despite being anticoagulated following all the guidelines available, our patient continued presenting recurrent VTE until we finally decided to consider that as a Palbociclib induced adverse event of grade 3 and reduced the dose of this accordingly (following the guidance of common terminology criteria for adverse events version 5.0 published in November 2017).

Since then, she has continued on treatment, coping well without any further issues and maintained on rivaroxaban 20mg daily.

Her recent CT scan (>1 year after the reduction) continues stable and without any evidence of any new pulmonary emboli.

To our knowledge there is no other similar case published.

Learning points

- Patients with cancer are at a higher risk of recurrent VTEs despite appropriate anticoagulation with the subsequent risk of death.
- Oncologists should be fully aware of the role of the anticancer treatments as sources of VTEs in these patients.
- CDK4/6 inhibitors, such as Palbociclib, are a recent incorporation into the anticancer arsenal which might produce VTEs.
- In case of recurrent VTE in a correctly anticoagulated cancer patient, oncologists should think about this being an adverse event and try to manage it by reducing the dose of the anticancer treatment appropriately.

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Many thanks to our patient for her collaboration with us in getting her case published. In fact, she would like to have her opinion seen.

"As this case shows, following a CT scan in later 2017 it was discovered that I had secondary breast cancer for which I was given Palbociclib 125 mg per day.Â The CT scan also found a pulmonaryÂ Â embolism.Â

I was immediately put onto Dalteparin. Not a great experience as too many injections. My tummy hurt. Several CT scans continued to show new embolisms and my anticoagulants were changed several times but none of them seemed work as expected.Â

This series of events led to a long time of worries and fears. I was feeling extremely vulnerable and it was finally suggested that I should have a decreased dosage of Palbociclib,Â 100 mg. I was initially reluctant but after yet another CT scan the embolism had gone and I was reviewed by my oncologist who changed my Dalteparin to Rivaroxaban.Â Since then I have had no further problems. I am happy to share my experience with others if this can help. "

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