Cancer and Clotting: Two Sides of the Same Coin?

Doctors interested in taking care of cancer patients must complete specialized training after their residency in internal medicine. This subspecialty training is called a fellowship and usually involves training in both hematology (study of blood disorders, including abnormal clotting and bleeding) and oncology (cancer). These two areas are pretty different, leading some to question why they are not split up into two completely different specialty training programs. For those of us who end up taking care of patients with solid tumors, we often question whether all of this hematology training has much value in our day to day practice.

Increasingly, though, links between clotting and cancer are emerging. As I result, I find myself going back to something that I found a lot less interesting during my training than I do now: the clotting cascade.

![Clotting Cascade Diagram]

Efficient clotting has been essential to our survival: without it, we would risk fatal bleeding with every scrape. Defects in this system lead to the disease hemophilia (Greek for loves to bleed), a disorder characterized by prolonged bleeding after minor trauma. Advances in the treatment of this disease have been a direct result of knowing which clotting factor (denoted by the roman numerals in the figure) is missing and then replacing it.

In cancer, we are usually dealing with excess clotting rather than bleeding; unfortunately, the reasons for this link aren’t as simple as an excess of a single factor. We have known for a
long-time that blood clots are associated with cancer. In fact, patients with an unexplained blood clot are up to ten times more likely to harbor a cancer than those with no clots or someone with a blood clot and a known cause for it. Increasingly, we are realizing that this is more than just a casual association: it appears that the clotting cascade may facilitate the growth of cancer even as cancer fuels clotting.

One of the end-products of the cascade is a protein called fibrin, which links together to form a tough mesh. Very useful for clot formation and for cancer survival, it turns out. This mesh may provide a nest that protects cancer cells as they grow and invade. Cancer researchers are often amazed that cancer cells are able to detach and make the trip through the bloodstream, constantly in danger of destruction by our body’s immune cells. Then, they have to arrive in a hostile, new tissue and somehow establish a blood supply. Fibrin may help by surrounding and protecting these fragile migrating cancer cells, preventing immune detection and attack. Fibrin may also draw new blood vessels to cancer cells and provide a platform on which the endothelial cells that form blood vessels can grow. Interestingly, cancers implanted into mice deficient in fibrin were unable to form metastases. Key players in the clotting cascade, such as tissue factor (TF) may also directly stimulate pathways involved in cancer growth and survival.

So, if the clotting process drives cancer growth, can we help patients with cancer by inhibiting the clotting process? Currently, we use anticoagulants to treat cancer patients who have developed a blood clot. Low molecular weight heparins such as Lovenox or Fragmin (both administered by subcutaneous shots) are preferred over Coumadin (oral) because of increased effectiveness at preventing recurrent clots in cancer patients. The first question is, given the high risk of blood clots, should we be giving prophylactic anticoagulation to all cancer patients? The recently completed PROTECHT trial randomized patients with solid tumors who were undergoing chemotherapy to either placebo or the injectable anticoagulant nadroparin. The study found that patients on the anticoagulant were half as likely to develop a blood clot. But the numbers who developed clots were small, only 4% in the placebo group compared to 2% in the nadroparin group.

The results for the lung cancer patients in the trial were more striking, with a 9% risk of developing a clot in the placebo group compared to 3.5% in the treatment group. Serious side effects were no more common with nadroparin than placebo. There was no difference in survival between the two groups though the authors note that patients remained on nadroparin...
for a relatively short time (median 4 months) which might make it difficult to see an effect on survival.

Other investigators have suggested that, independent of the reduction in blood clots, anti-coagulants may have a direct anti-cancer effect. Some of the most intriguing results have come from studies in small cell lung cancer (SCLC), a disease where we can definitely use some new ideas. In one small trial, patients with SCLC were randomized to chemotherapy or chemotherapy plus the anticoagulant dalteparin (Fragmin). Those treated with anticoagulation and chemo had a median survival of 13 months compared to 8 months for those on chemo alone. Even though only 84 patients were included, the results were statistically significant (p = .01).

I was thinking about all of this when I happened to hear a fascinating presentation at a recent meeting in Boston. Dr. Caroline Dive was presenting her work on circulating tumor cells and she discussed some interesting findings in patients with SCLC. She described discovering large numbers of tumor microemboli in a patient who had a particularly aggressive tumor. I wondered if this may be a key to the early dissemination of SCLC and the difficulty of curing this disease. If SCLCs are particularly good at making fibrin, this may explain both their propensity for dissemination and why anti-coagulants might have an effect on survival in this disease.

Part of making progress in cancer involves improving our supportive care. Certainly, we have been able to help patients by using drugs to reduce the risk of neutropenia or severe nausea with chemotherapy. Chemotherapy may actually contribute to the pro-clotting environment in cancer patients. Given the results of the PROTECHT study for lung cancer, I’m wondering if we should add prophylactic anticoagulation to our arsenal of supportive care. At the very least, I think that the issue of anticoagulation in lung cancer patients deserves further study and attention, even at the risk of having to learn the clotting cascade all over again.