Comment on Becattini et al, page 900

Rivaroxaban after laparoscopic cancer surgery

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Reduction of thrombotic risk after surgery is a long-established clinical practice standard, but evidence is lacking in some specific settings. In this issue of *Blood*, Becattini et al[1] publish the results of PROLAPS-II, a randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of extended prophylaxis with rivaroxaban after laparoscopic surgery for colorectal cancer.

Venous thromboembolism (VTE) is a common adverse event following surgery, particularly in patients with cancer.[2] The risk is related to the nature of the surgery, presence of underlying cancer, and comorbidities. Extended (4 weeks total) anticoagulation with low-molecular-weight heparin (LMWH) is now standard of care for patients undergoing open abdominal or pelvic cancer surgery who are not at high risk for major bleeding complications.[3] Those guidance statements were based on studies of prophylactic anticoagulation in open surgery, not laparoscopic surgery, and used LWMH rather than a direct oral anticoagulant (DOAC).[3-5] Unanswered questions include the following: does the risk:benefit calculus for prolonged anticoagulation (4 weeks vs 7 days) apply to laparoscopic cancer surgery, and can a DOAC be used for at least part of the course of anticoagulation?

In this issue of *Blood*, Becattini and colleagues report on the PROLAPS-II study, a randomized, double-blind, placebo-controlled study assessing the efficacy and safety of extended prophylaxis with rivaroxaban after laparoscopic surgery for colorectal cancer. As short-term prophylactic anticoagulation after laparoscopic surgery for colorectal cancer is currently accepted as standard of care, all patients received prophylaxis with LMWH starting 12 to 24 hours after surgery, continued until randomization at 7 ± 2 days, as soon as patients were able to eat. Patients received once-daily rivaroxaban 10 mg or placebo for an additional 3 weeks. The primary endpoint was confirmed VTE or VTE-related death at 28 ± 2 days and included a venous ultrasonography of the lower limbs at the endpoint. Thus, the study was evaluating the potential efficacy and safety of postoperative anticoagulation for 4 weeks, rather than 1 week, and use of rivaroxaban during that extended period.

Superior efficacy was demonstrated in the rivaroxaban arm, with a significant reduction of confirmed VTE or VTE-related death from 3.9% in the placebo group to 1.0% in the rivaroxaban-treated group. Bleeding was infrequent, with 2 surgical-site major bleeds in the rivaroxaban arm (0.7%) per the International Society of Thrombosis and Haemostasis definition,[6] which is consistent with anticipated major bleeding rates with LMWH.[7] The overall rate of combined major bleeding and clinically relevant nonmajor bleeding was the same in both arms.

Thus, PROLAPS-II nicely answers that for patients undergoing laparoscopic surgery for colorectal cancer, extending anticoagulation prophylaxis from 7 to 28 days reduces the relative risk of VTE by ~75%, with a reassuring safety signal. Furthermore, rivaroxaban may be used after the first week of postoperative anticoagulation.

To address the role of anticoagulation for treatment or prophylaxis of VTE in a given situation, one should consider the following topics.

In patients undergoing laparoscopic surgery for colorectal cancer, extending prophylactic anticoagulation from 7 to 28 days significantly reduces the risk of VTE. The number needed to treat (NNT) is 34 patients for the primary study outcome, which is clinically relevant and justifiable. Comorbidities and patient-specific factors need to be considered, of course.

The NNT to prevent 1 symptomatic VTE was relatively high at 91. However, if the favorable safety signal of prophylactic rivaroxaban is observed in expanded real-world practice, then the use of prophylactic rivaroxaban in this setting should be incorporated into practice.

Prophylactic dose rivaroxaban has now been shown to be an acceptable choice in this specific setting of laparoscopic surgery for colorectal cancer, at least after postoperative day 7 and once the patient is able to eat, until 4 weeks after surgery. This is an extremely relevant finding. Abdominal surgery involving the gastrointestinal (GI) tract could potentially impact absorption and may also be associated with an increased risk of GI bleeding.[8] This study provides reassurance that rivaroxaban is effective and safe, at least in this specific situation.

As LMWH requires subcutaneous injection by the patient or caregivers, and much of the postoperative anticoagulation course is usually administered at home, an oral alternative is certainly desirable. In addition, compliance with self-administration of LMWH is known to be poor; presumably rivaroxaban compliance will be better.

This study evaluated and validated prophylactic dose LMWH for the initial 7 days after surgery and prophylactic rivaroxaban 10 mg for an additional 3 weeks. This study does not provide guidance for therapeutic doses of anticoagulation in the 28-day postoperative period. Patients with another indication for anticoagulant therapy after surgery, such as prior VTE, mechanical valve, or atrial fibrillation, were explicitly excluded. Use of therapeutic dose anticoagulation in the perioperative setting, vs prophylactic dose, has been shown to be associated with a marked increase in the risk of bleeding.[9]

This study compares only 2 timepoints, 7 days vs 28 days, and the 28-days timepoint was superior. A randomized clinical trial cannot practically address a wide range of prophylactic anticoagulation durations. The 28-day period of this

study is in-line with other major surgical procedures.

One must be cautious and consider the exclusion criteria of the study, such as increased risk of bleeding, cerebral metastases, or other risks of intracerebral bleeding, or renal or liver dysfunction. The study also excluded patients with an underlying indication for anticoagulation, as prophylactic doses of anticoagulation may not be sufficient for the other indication. Individual patients may also have other comorbidities precluding safe and effective use of prophylactic rivaroxaban.

The field of anticoagulation has certainly become more nuanced since the introduction of heparin and warfarin, well over 60 years ago. When there was 1 choice available, the choice was simple. With the expanding number of indications, therapeutic options, and dosing regimens, we have the ability and opportunity to be more selective and optimize safety and efficacy.

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TRANSPLANTATION

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Playing with fire: unrecognized AA genetic predisposition

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In this issue of *Blood*, McReynolds et al[1] report a study of extended genetic testing that revealed clinically unrecognized forms of germline aplastic anemia (AA) or inherited bone marrow failure disorder (IBMFD) in patients undergoing hemopoietic cell therapy (HCT). Their cohort of 732 patients with AA underwent either a related or unrelated HCT over nearly 30 years in centers affiliated with the Center for International Blood and Marrow Transplant Research. All patients had a blood sample available for whole-exome analysis.

AA, the quintessential disorder of bone marrow failure, can be acquired or inherited (inherited bone marrow failure disorder [IBMFD]). Acquired forms are usually immune-mediated, whereas inherited forms may be caused by DNA repair defects (Fanconi anemia), short telomere syndromes (dyskeratosis congenita), ribosomopathies (Shwachman-Diamond and Diamond-Blackfan anemia), or other germline mutations (*GATA2*, *RUNX1*). Acquired severe AA (SAA) is preferentially treatedwith allogeneic HCT (vs immunosuppressive therapy [IST]) in patients with a suitable donor. Immunosuppression is not a rational therapeutic option in inherited AA, and HCT, when appropriate, requires optimization for the underlying disorder. Thus, knowledge of any germline etiology of the patient's AA has therapeutic relevance.

McReynolds et al used a curated list of 104 genes relevant to hematopoietic differentiation, DNA damage response, telomere, and ribosome biology. After variant selection, they studied the correlation between potential germline mutations and specific post-transplant outcomes. With a rigorous statistical approach, they identified single-nucleotide variants and copy-number variants in 48 patients (6.6%). One-third were adult patients; however, only 3 patients with identified mutations were >40 years of age.

Patients with AA who had genetic evidence of previously unrecognized IBMFD present in the pre-HCT sample experienced worse survival, irrespective of the transplant platform (myeloablative or reduced intensity [RIC] conditioning) or donor relationship. The increased mortality was attributed to organ failure, with the highest rates in those patients with