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Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: Results from a multicenter, randomized, open-label study

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ABSTRACT

Background: Enoxaparin sodium (enoxaparin) is used worldwide for the prevention of venous thromboembolism (VTE). Registration trials of enoxaparin have been conducted primarily in Caucasian populations, and its preventive use in Japanese patients has yet to be established. To address this, we evaluated the efficacy and safety of postoperative enoxaparin in Japanese patients undergoing surgery for abdominal cancer.
Methods: This multicenter, open-label study randomized 151 Japanese patients undergoing curative surgery for abdominal cancer to enoxaparin 20 mg twice daily for 14 days, started 24–36 hours after surgery (n = 113) or intermittent pneumatic compression (IPC) as a reference (n = 38). IPC was performed at least once in both groups between randomization and surgery. The primary efficacy endpoint was the incidence of VTE in the modified intention-to-treat (mITT) population. The primary safety outcome was the incidence of any bleeding during treatment and follow-up.
Results: Incidence of VTE was 1.2% (95% CI, 0.03–6.53%) (1/83 patients) in the enoxaparin group and 19.4% (95% CI, 7.45–37.47%) (6/31 patients) in the IPC group. In the safety population, 10/109 patients in the enoxaparin group (9.2%; 95% CI, 4.49–16.23%) and 3/38 patients in the IPC group (7.9%; 95% CI, 1.66–21.38%) experienced a bleeding event. There were no cases of fatal bleeding or bleeding into any critical organ.
Conclusions: These favorable efficacy and safety data support the use of enoxaparin (20 mg twice daily for 14 days started 24–36 hours after surgery) in Japanese patients undergoing abdominal or pelvic cancer surgery.

Introduction

Patients with cancer requiring curative abdominal surgery are considered to be at a particularly high risk of venous thromboembolism (VTE) [1,2]. In a survey of Western clinical trials assessing thromboprophylaxis in surgical patients with cancer, the incidence of deep-vein thrombosis (DVT) in untreated patients was 29% [3]. In the same type of survey, the incidence of VTE was similar to that observed in a multicenter, prospective, epidemiologic study conducted in Japan, where the estimated incidence of VTE in patients following abdominal surgery without prevention was 24.3% [4].

Randomized controlled trials conducted in a range of surgical settings over the last 25 years have clearly demonstrated that enoxaparin is associated with lower rates of VTE than placebo or elastic compression, without compromising patient safety [5–9]. In patients undergoing abdominal surgery, two randomized double-blind trials demonstrated that enoxaparin 40 mg once daily achieved similar safety and efficacy in preventing VTE to unfractionated heparin three times daily [10,11]. Specifically, of 631 evaluable patients undergoing surgery for abdominal or pelvic malignancy in the Enoxaparin and Cancer (ENOXACAN) I study, 14.7% and 18.2% in the enoxaparin and heparin groups, respectively, had a thromboembolic complication [10]. In the ENOXACAN II study, Caucasian patients undergoing planned curative open surgery for abdominal or pelvic cancer received enoxaparin 40 mg once daily for 6–10 days before randomization to either enoxaparin or placebo for a further 21 days. Patients randomized to enoxaparin had a significantly lower incidence of VTE than those randomized to placebo (4.8% vs 12.0%; p = 0.02), while there was no significant difference between the groups in the rate of bleeding events [12].

Randomized controlled studies in orthopedic surgery have demonstrated that enoxaparin 20 mg twice daily has a good safety profile and is effective for the prevention of VTE in Japanese patients who have undergone total hip or knee replacement [13]. In these studies, enoxaparin significantly decreased VTE compared with placebo.

We therefore aimed to evaluate the efficacy and safety of enoxaparin for the prevention of VTE in the setting of abdominal surgery in a Japanese population, using the dosage regimen already approved for use in Japanese patients undergoing orthopedic surgery

Abbreviations: bid, twice daily; BMI, body mass index; CI, confidence interval; DVT, deep-vein thrombosis; IPC, intermittent pneumatic compression; mITT, modified intention-to-treat; NSAID, nonsteroidal anti-inflammatory drug; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

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(20 mg twice daily). To give the results of this open-label study an epidemiologic perspective, a group of the patients received mechanical prophylaxis with intermittent pneumatic compression (IPC) as a reference; IPC is one of several nonpharmacologic interventions currently widely used in Japanese medical practice.

Materials and methods

We conducted a multicenter, open-label, Phase III study at 36 medical institutions in Japan between March and December 2007 (NCT00723216). The study was approved by the appropriate Institutional Review Boards and was undertaken in full compliance with the principles of Article 14-3 and Article 80-2 of the Pharmaceutical Affairs Law, MHW Ordinance on Good Clinical Practice, and Declaration of Helsinki. An independent expert panel evaluated venography, chest X-rays (if appropriate), lung ventilation/blood scintigraphy, pulmonary angiography, and computerized tomography in a blinded manner. Written informed consent was obtained from all patients before their participation in the study.

Patient selection

Male or female patients were eligible for the study if they were ≥40 years old (no upper age limit was applied) and were undergoing a planned, curative laparotomy for cancer of >45 minutes duration. Abdominal cancer surgery was defined as including all intrapelvic (i.e. descending colon, sigmoid colon, rectum, bladder, prostate, uterus, fallopian tube, and ovary) and upper intra-abdominal (i.e. stomach, duodenum, jejunum, ascending colon, transverse colon, liver, gallbladder, bile duct, pancreas, kidney, urinary duct, and adrenal gland) operations between the diaphragm and the pelvic floor. Only patients with a life expectancy of 6 months or more after surgery were considered for study enrollment.

Patients were excluded from the study if they only received surgery under laparascopy or other endoscopic conditions, had a hypersensitivity to heparin or thrombocytopenia due to heparin, had clinical signs of DVT at screening or evidence of thromboembolic disease within 1 year before surgery, or had received systemic chemotherapy within 3 weeks (or radiotherapy within 15 days) before study drug initiation. Women of childbearing potential, together with those who were pregnant or lactating, were also excluded. Use of the following therapies was prohibited from postoperation to completion of venography: aspirin, other antiplatelet agents, dextran, other anticoagulants, thrombolytics, estrogen, and progesterone. In addition, the use of nonsteroidal anti-inflammatory drugs was not permitted within 48 hours after surgery, and the administration of a postoperative epidural catheter or spinal analgesia was discouraged from 2 hours before the first dose of study drug through to the completion of venography. In patients for whom the investigator judged epidural anesthesia necessary, the study protocol specified catheter withdrawal at least 10–12 hours after the last enoxaparin administration.

Interventions

Patients were randomized in a 3:1 ratio to receive either a subcutaneous injection of enoxaparin 20 mg twice daily or IPC prophylaxis alone (Fig. 1). Enoxaparin was started 24–36 hours after surgery and continued for 14 days (and for at least 7 consecutive days). The duration of IPC treatment in the enoxaparin group was left to the discretion of the investigator; however, all patients were to receive at least one course of postsurgical IPC before administration of the first enoxaparin dose. The IPC-alone group was set as the reference for VTE incidence during the study period but was not intended to be compared statistically with the enoxaparin group.

Assessments and outcome definitions

The safety population was defined as all patients who received at least one randomized study treatment. Those in the safety population who had appropriate VTE imaging tests comprised the modified intention-to-treat (mITT) population.

The primary efficacy endpoint was the incidence of VTE (DVT or pulmonary embolism [PE]) in the mITT population. DVT was identified by systematic venography performed within 1 day after the final administration of treatment. DVT was further classified as proximal DVT or distal DVT, based on the location of thrombus. Proximal DVT was diagnosed if the thrombus was in the popliteal or more proximal veins while the distal DVT was diagnosed if thrombus was found in the calf veins. Confirmation by ultrasonography was accepted when there were clinical signs suggestive of symptomatic DVT and when it was impossible to conduct venography. PE was confirmed by ventilation/perfusion lung scan, pulmonary angiography, or computerized tomography.

The primary safety endpoint was the incidence of all bleeding events, which was a composite endpoint comprising the incidences of major and minor bleeding events. Bleeding was classified as major if the event met at least one of the following criteria: resulted in death; was clinically overt (required transfusion of at ≥2 units (400 mL) of packed red blood cells or whole blood, or decreased hemoglobin levels by at least 2 g/dL); was retroperitoneal, intracranial, or intraocular; or resulted in serious or life-threatening clinical events (e.g. myocardial infarction, cerebrovascular accident) or required surgical or medical intervention to control the event. Bleeding was classified as minor if the event did not meet any of the major bleeding criteria but resulted in one of the following: epistaxis lasting ≥5 minutes or epistaxis that required treatment; ecchymosis or hematoma ≥5 cm diameter; hematuria not associated with intubation of a urinary catheter; gastrointestinal hemorrhage not related to intubation or nasogastric tube placement; and subconjuctival hemorrhage requiring treatment discontinuation. The secondary safety endpoint was the incidence of adverse events (including abnormal changes in laboratory values). All patients were followed up at 14 days after surgery. All adverse events were coded using the Medical Dictionary for Regulatory Activities (version 10.1), as recommended by the International Conference on Harmonization guidelines [14].

Statistical considerations

It was previously determined that enoxaparin 20 mg twice daily was associated with a 50% reduction in the risk of VTE relative to placebo in patients who had undergone total hip or knee replacement [13]. As the estimated incidence of VTE in Japanese patients undergoing abdominal surgery was 24.7% [4], it was assumed that the event rate would be 12% in the enoxaparin 20 mg twice-daily group in this study. The study would therefore require a sample size of 73 patients in the enoxaparin group to achieve a precision of ±7.5% (range of 15% in the 95% confidence interval [CI]). Assuming that the rate of nonevaluable patients for primary efficacy would be 20%, we planned to enroll a minimum of 92 patients in the enoxaparin group. Based on observations from clinical practice, we planned to enroll 33 patients for the IPC reference group.

Results

Patient disposition and analysis populations

A total of 151 patients were randomized of whom 147 received at least one study intervention and were therefore included in the safety population (Fig. 2). Of these 147 patients, 17 (11.6%) had no VTE measurement and 16 (10.9%) had an inadequate VTE assessment. The mITT population thus comprised 114 patients.