Upper-extremity deep vein thrombosis related to central venous port systems implanted in cancer patients

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ABSTRACT. The purpose of the current study was to evaluate the incidence and course of upper-extremity deep vein thrombosis (UEDVT) related to an implanted central venous port (CV-port) system in cancer patients. From July 2007 to July 2008, 92 consecutive patients who underwent implantation of a CV-port for chemotherapy for colorectal cancer were prospectively enrolled in the study. All patients were examined at prescribed intervals by ultrasonography (US) to estimate the incidence of catheter-related venous thrombosis. We categorised ultrasound diagnosis into three types: Type 0, no thrombus; Type I, thrombi around catheter without obstruction of venous flow; Type II: thrombi with obstruction of venous flow. Upon initial ultrasound examination, 25 cases (27%) were categorised as Type 0, 64 (70%) as Type I and III (3%) as Type II. Of the 64 Type-I cases, 4 cases worsened to Type II within a month, and 3 others (including 1 patient who developed pulmonary embolism) became Type II after 1 month. Of the other Type-I cases, 12 cases improved to Type 0 and 45 cases remained Type I. All 10 patients categorised as Type II underwent anticoagulant therapy and resumed their chemotherapy without exacerbations of thrombosis. In cancer patients undergoing long-term chemotherapy, there is an unexpectedly high prevalence of catheter-related UEDVT, which can be detected by ultrasound at an early stage after implantation of a CV-port. Given that cancer patients with UEDVT may have worse outcomes than those without, clinicians should consider careful monitoring for UEDVT and introducing anticoagulant therapy.

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Patients with cancer are more prone to develop deep vein thrombosis (DVT) because of the hypercoagulable state caused by the malignancy and other additive risk factors, such as mechanical injury of the venous endothelium caused by the use of intravenous catheters and irritation of vessel walls by chemotherapy. In cancer patients who develop DVT, the risk of death is more than three times greater than it is for patients without cancer who have venous thromboembolism (VTE) [1, 2] and for those with cancer who have no VTE [3].

Upper-extremity deep vein thrombosis (UEDVT) was long considered to be a benign and self-limiting condition. With the increasingly common use of intravenous catheters, however, UEDVT has been found to be more common than previously reported and to cause significant complications, including pulmonary embolism (PE) and superior vena cava syndrome [4].

Muñoz et al [5] reported that cancer patients with UEDVT had worse outcomes than those with lower-limb DVT [5]. Of patients with UEDVT, 45% had DVT related to catheters, including central venous port (CV-ports) systems implanted in the chest wall [5].

CV-ports have been widely used in cancer patients undergoing long-term chemotherapy, resulting in the need

to manage catheter-related complications. However, there is little information on the clinical characteristics and outcomes of patients with UEDVT. Few investigators have used prospective Doppler ultrasonography screening for catheter-related DVT, and therefore the incidence of catheter-related DVT is probably underestimated.

The purpose of this prospective study was to evaluate the incidence and course of catheter-related UEDVT in cancer patients using ultrasound.

Methods and materials

Study population and follow-up

From July 2007 to July 2008, we enrolled 92 consecutive patients who underwent implantation of a CV-port for administration of chemotherapy for metastatic colorectal cancer at Cancer Institute Hospital, Tokyo, Japan. All of these patients underwent ultrasound scans within 1 month of implantation of the CV-port and were followed up by ultrasound after an interval of 1–3 months if thrombi were detected. During follow-up, ultrasound was performed at the anatomical location where patients complained that there was something wrong with the upper extremity on the implanted side.

Before any study procedures were performed, written informed consent was obtained from each patient. Our

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Figure 1. Type I findings upon ultrasound of the internal jugular vein and subclavian vein. The images show (a) thrombi (arrows) around the indwelling catheter but (b) no obstruction of venous flow.

ethics committee approved this study, which complied with the principles of the Declaration of Helsinki.

Imaging method and clinical definitions

All ultrasound scans were performed with a diagnostic ultrasound system, model SSA-770A (Toshiba, Tokyo, Japan), by one of three radiologists (SY, YF and YY) using an 8.5-MHz linear-array transducer. Longitudinal and transverse ultrasound scans of the internal jugular vein and the subclavian vein were obtained. A thrombosis was identified on the basis of the following ultrasound signs: echogenicity around the catheter; lack of normal vein compressibility; lack of colour signal from the vessel on the colour Doppler scan; and lack of signal from the vessel on the spectral Doppler scan.

The ultrasound diagnosis was categorised as one of three types: Type 0 showed no thrombus, Type I had thrombi around the catheter but without obstruction of venous flow (Figure 1) and Type II had thrombi around the catheter along with obstruction of venous flow (Figure 2). We

censored follow-up in the case of Type 0, continued follow-up in the case of Type I and treated with anticoagulatory therapy and continued follow-up in the case of Type II.

Central venous port procedures

All the CV-port implantations were performed in the interventional radiology suite. The subclavian vein was directly punctured with an 18-G Teflon IV catheter under venographic or ultrasonographic guidance. Subsequently, with a 0.035-inch guide wire, the catheter tip was positioned in the lower part of the superior vena cava and an infusion port was placed within a subcutaneous pocket created on the anterior chest wall. An indwelling catheter (6-French Anthron P-U catheter; Toray, Tokyo, Japan) was inserted and connected to the infusion port (P-U Celsite port; Toray). After implantation, the devices were flushed routinely for every patient by injections of heparin at various intervals of between 1 and 4 weeks. No anticoagulatory treatment was administered unless thrombosis occurred.

Figure 2. Type II findings upon ultrasound of the internal jugular vein and subclavian vein. The images show (a) thrombi (arrows) around the indwelling catheter along with (b) obstruction of venous flow.

Statistical analysis

Demographic data and clinical features were analysed using descriptive methods. Quantitative variables were summarised using means and standard deviations. Categorical variables were summarised as counts and percentages, and were compared using the χ^2 test. The level of statistical significance was set at $p < 0.050$.

The statistical analysis was performed using SPSS for Windows 15.0J (SPSS Inc., Chicago, IL, USA).

Results

Patients characteristics

CV-ports were implanted in 92 consecutive patients (44 men and 48 women; mean age 58.3 years; age range 16–74 years) and were used to administer chemotherapy for colorectal cancer. All patients received chemotherapy, including the combination of bevacizumab and either the FOLFOX4 (containing oxaliplatin, leucovorin and fluorouracil) or FOLFIRI (containing irinotecan, leucovorin and fluorouracil) regimen [6, 7].

Implant success and follow-up

The technical success rate was 100% for placement of the CV-port devices in the chest. Of the 92 insertions, 89 were performed via the right subclavian vein and 3 were performed via the left subclavian vein.

The mean follow-up period for the 92 implantations was 76 days (range 3–473 days) and the total number of ultrasound examinations was 272 (1–9 per patient).

Course of upper-extremity deep vein thrombosis

Upon initial ultrasound examination, 25 cases (27%) were categorised as Type 0, 64 (70%) as Type I and III

(3%) as Type II (Figure 3). Of the 64 Type I cases, 4 cases worsened to Type II within a month and 3 others (including 1 patient who developed pulmonary embolism) became Type II after 1 month of follow-up. Of the other Type I cases, 12 cases improved to Type 0 and 45 cases remained Type I. Of the 64 Type I cases, 13 cases were followed more than 6 months. Of these, 3 cases improved to Type 0 over the 6-month follow-up period and the other 10 cases remained Type I.

Of the 10 patients categorised as Type II, at either the initial or follow-up examination, 5 had some signs or complaints related to UEDVT and the other 5 had no symptoms.

The mean interval between catheter placement and the onset of Type II thrombosis was 27.9 days (range 7–77 days). In symptomatic cases, the mean interval was 37.2 days (range 11–77 days), and in asymptomatic cases, 18.6 days (range 7–42 days). There was no significant difference between these values ($p = 0.24$).

In the Type II patients, the port removal was not performed because the CV-port functioned correctly. All 10 patients who underwent anticoagulatory therapy resumed their chemotherapy without exacerbations of thrombosis.

Discussion

To determine the true incidence of venous thrombosis, we performed a prospective per-protocol study of sequential venous duplex sonography in all patients with a CV-port. Our study showed that 67 (73%) of 92 patients with a CV-port had catheter-related thrombi and 10 (11%) showed obstruction of venous flow, which required anticoagulatory therapy.

Most of the previously reported studies investigating catheter-related DVT were based on clinically symptomatic thromboses, and thus the incidence of catheter-related DVT was unclear and probably underestimated [8, 9]. The prevalence rates from these studies were higher than those

Figure 3. Flow chart showing the course of findings upon ultrasound.

in reports based on retrospective clinical criteria. By contrast, the rates determined in our study are similar to those from several prospective studies [10].

One reason for the higher rates of thrombosis in our study was the population selected. For instance, cancer patients with adenocarcinomas may be at greater risk of catheter-related thrombosis than patients with other types of malignancies, potentially warranting the use of thromboprophylaxis in select cancer subgroups.

Historically, UEDVT was considered to be a benign and self-limiting condition, but recent reports have demonstrated that UEDVT may have significant complications. In addition, among all types of patients with UEDVT, those with cancer have the worse outcome [5]. In the management of cancer patients, measures for preventing and screening for UEDVT should be considered a matter of critical importance.

When UEDVT is confirmed, anticoagulant therapy is the treatment of choice, but there is no consensus on the optimal management of UEDVT because spontaneous resolution of thrombosis can occur. However, van Rooden et al [11] reported that the presence of asymptomatic thrombosis upon Doppler ultrasound was associated with a seven fold increase in the risk of developing symptomatic thrombosis. We administered anticoagulatory therapy to patients in whom venous flow was disturbed, regardless of symptoms. In this way, all of these patients resumed their chemotherapy without exacerbations of thrombosis.

Of the follow-up patients with thromboses who did not receive anticoagulatory therapy, we observed one patient who subsequently suffered symptomatic PE. Therefore, we must consider the use of anticoagulation therapy for all patients with UEDVT, even when they are asymptomatic.

Of the 10 patients who developed type-2 UEDVT, 7 patients did so within the first month after CV-port implantation, with a mean interval of 27.9 days between catheter placement and the development of catheter-related UEDVT, in accordance with the findings in previously reported studies [10]. Some authors believe that catheter-related DVT is triggered by trauma caused by the initial venous puncture, and this mechanism could account for the early onset of catheter-related DVT [10]. We believe that early screening for UEDVT is beneficial to cancer patients with a CV-port. Furthermore, upon clinical follow-up, clinicians must pay close attention to what might appear to be trivial signs and symptoms involving the arm on the implanted side. We detected UEDVT requiring treatment in three patients who reported only a sense of discomfort, without oedema or swelling.

Conclusions

In cancer patients undergoing long-term chemotherapy, there is an unexpectedly high prevalence of catheter-related UEDVT, which can be detected by ultrasound at an early stage after implantation of a CV-port. Given that cancer patients with UEDVT may have worse outcomes, clinicians should consider careful monitoring for UEDVT and the introduction of anticoagulant therapy upon thrombus detection, with or without symptoms.

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