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LOW-DOSE SYSTEMIC THROMBOLYTIC THERAPY FOR DEEP VEIN THROMBOSIS IN PEDIATRIC PATIENTS

Sarah E. Leary, MD^{1,*,#}, Virginia L. Harrod, MD, PhD^{1,*,#}, Pedro A. de Alarcon, MD^{1,#}, and Ulrike M. Reiss, MD^{1,#}

¹Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Reduction of thrombus size and recanalization of vessels after deep vein thrombosis (DVT) are important goals to prevent recurrent thrombosis and development of post-thrombotic syndrome. Thrombolysis is effective but concern for bleeding complications has limited its use in children. We retrospectively analyzed data for children with DVT treated with a low-dose systemic tissue plasminogen activator (tPA) regimen. Twenty-three pediatric patients (12 males and 11 females, median age 12 years) received low-dose systemic tPA, initiated at 0.03 to 0.06 mg/kg/hr for a median of 24 hours (range 12–48 hours). Of 20 patients imaged within 24 hours of therapy, six (30%) showed partial to complete thrombus resolution. Eight patients subsequently received increased tPA at 0.12 mg/kg/hr for an additional 24 hours (range 12–36 hours). Six of these eight (75%) patients responded to the increased dose. The overall response at the end of thrombolytic therapy was 59% (13/22). Two bleeding complications without serious sequelae occurred. Low-dose tPA administration leads to a substantial response rate although the risk of bleeding remains unclear. A prospective multicenter trial of low-dose thrombolytic therapy in children with acute DVT is warranted.

Keywords

Children; Thrombolysis; Thrombosis; Tissue plasminogen activator

INTRODUCTION

Deep vein thrombosis (DVT) in children is relatively rare but causes serious acute and chronic complications with significant morbidity, such as clot extension or recurrence, pulmonary embolism, and chronic venous insufficiency. Thrombosis-related mortality is 1%–4%. Thrombosis recurs in 6.5%–21% of patients, and more than 50% of patients with pulmonary embolism are diagnosed with co-existing DVT.[1,2] Post-thrombotic syndrome (PTS) is a long-term sequela developing in 10%–70% of children with DVT, but data on long-term outcomes are scarce.[1,3–7] Therapeutic factors that affect the incidence of PTS include speed and completeness of clot resolution, prevention of recurrent thrombosis with anticoagulation therapy, and supportive care such as long-term use of compression stockings and frequent elevation of the affected extremity.[8–10] Rates of PTS, thrombus recurrence,

Correspondence to: Ulrike M. Reiss, MD, Department of Hematology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, Phone: 901-595-4753, Fax: 901-595-2952, ulrike.reiss@stjude.org.

*Sarah E. Leary and Virginia L. Harrod contributed equally to this work.

#Current address:

Sarah E. Leary: Hematology/Oncology, Seattle Children's Hospital, Seattle, WA

Virginia L. Harrod: Pediatric Hematology/Oncology, *Specially for Children, Dell Children's Medical Center of Central Texas, Austin, TX

Pedro A. de Alarcon: Department of Pediatrics, University of Illinois College of Medicine, Peoria, IL

and pulmonary embolism are influenced by the initial management of thrombosis, but the role of thrombolysis within an initial treatment regimen for children with DVT has not been fully defined.

The currently recommended standard therapy for DVT in adults and children is anticoagulation with unfractionated heparin or low-molecular-weight heparin (LMWH), often followed by warfarin.[11–13] Systemic or catheter-directed medical thrombolysis can increase the speed and extent of clot resolution, thereby decreasing the risk of PTS. In adults, small series have suggested that thrombolysis is more effective than unfractionated heparin therapy in decreasing the risk of PTS without increasing the rate of bleeding complications.[10,14–16] A recent study comparing systemic thrombolysis with tissue plasminogen activator (tPA) (combined with mechanical thrombectomy in some patients) to standard anticoagulation alone in a highly selected cohort of children with occlusive proximal lower-extremity DVT and acute elevation of previously established prognostic biomarkers suggested that thrombolysis may significantly lower the incidence of PTS and reduce DVT-related morbidity.[17] However, many clinicians limit the use of tPA in children because of concerns about serious bleeding complications.[18–20] Low-dose tPA has been used to ameliorate the risk-benefit ratio.[21–24] In a multi-institutional study to determine the minimal effective dose of tPA in children, Wang et al. demonstrated that low-dose tPA (0.01–0.06 mg/kg/hr) had higher safety and efficacy than standard-dose tPA (0.1–0.5 mg/kg/hr) and suggested that low-dose systemic tPA is an equally effective alternative to standard-dose tPA but reduces risks of bleeding.[23]

We conducted a retrospective analysis of data on response and complications in children with acute DVT beyond the neonatal period who were treated by low-dose systemic tPA from December 2003 to May 2006 at St. Jude Children's Research Hospital (St. Jude) and Le Bonheur Children's Medical Center (LBCMC).

MATERIALS AND METHODS

Recommendations for use of low-dose thrombolytic therapy with tPA to treat DVT in children at St. Jude and LBCMC were developed in 2003 based on results of Wang et al.[23] and according to the 2001 ACCP guidelines.[25] Individualized treatment with tPA was recommended for patients with occlusive DVT of a major vein (axillary, subclavian, brachiocephalic, caval including right atrium, renal, hepatic, portal, iliofemoral veins). The treating physician decided the type of imaging study. Imaging studies were interpreted as per radiology standards. Contraindications to systemic tPA were central nervous system surgery, bleeding, or ischemia within 4 weeks. Surgery or an invasive procedure such as CVL placement or arterial puncture within 2 weeks; current active bleeding, mechanical ventilation, or uncompensated coagulopathy. A thrombophilia evaluation including Factor V Leiden, Prothrombin 20210, protein C, protein S, antithrombin, lipoprotein (a), homocysteine, lupus anticoagulant, anticardiolipin and anti-beta-2-glycoprotein I antibodies was recommended. Initiation with low-dose systemic tPA (0.06 mg/kg/hr) for 24 hr was recommended. If at 24 hr re-imaging showed no improvement of the thrombus, tPA dose was increased to 0.12 mg/kg/hr for another 24 hr. As per institutional approach chosen at that time, anticoagulation with heparin (unfractionated or LMW heparin) was initiated with tPA at therapeutic levels [partial thromboplastin time (PTT) 2–3 times normal, anti-Xa 0.5–1.0 IU/mL]. Platelet count and fibrinogen were monitored every 6 hr, and PTT or anti-Xa, fibrinogen, and plasminogen every 24 hr; D-dimer was not monitored. Transfusion of platelets or cryoprecipitate was recommended to keep platelets $>100 \times 10^9/L$ and fibrinogen $>100 \text{ mg/dL}$. Repeat imaging of any type was done at least every 24 hr and 3 months after therapy. Continued anticoagulation with LMWH or warfarin was recommended for 3–6

months or longer with clinical follow-up for signs and symptoms of PTS. Adherence to these guidelines was left to the treating physician's discretion.

This retrospective study was approved by the institutional review boards of St. Jude, Methodist Healthcare, and LBCMC. Eligible patients were identified from clinical databases from both institutions between December 2003 and May 2006. Pediatric patients with a diagnosis of acute DVT were included if they had received continuous low-dose systemic tPA (0.06 mg/kg/hr), and showed evidence of thrombus by ultrasound, computed tomography, venography, or echocardiography. Patients who received only site-directed tPA or standard (high-dose) tPA (0.1 mg/kg/hr) were excluded.

Major complications were defined as any medical event deemed life-threatening or requiring discontinuation of thrombolytic therapy. Minor complications were defined as any medical event requiring additional intervention, but allowing continuation of thrombolytic therapy. Expected side-effects of tPA such as minimal bruising or oozing at peripheral intravenous catheter sites were not recorded as complications. Reports of imaging studies were reviewed. Response was defined as complete (CR) if there was no evidence of thrombus on follow-up imaging, partial (PR) if there was improvement in blood flow or size of thrombus, and no response (NR) if the thrombus was unchanged. Responses were determined by investigators' interpretation of the clinical radiology report.

RESULTS

Patient and treatment characteristics

From December 2003 to May 2006, 23 pediatric patients (12 males) received low-dose systemic tPA for acute DVT (Table 1). Median age was 12 years (range 0.5–21.5 years). DVT involved the lower venous system in 10 patients and the upper in 13 patients. Eighteen patients had a central venous catheter (CVL) in place at the time of acute DVT, of whom 15 (83%) had a CVL-related veno-occlusive thrombosis. There were 14 patients with occlusive (oDVT), 7 with partially occlusive, and 2 with right atrial thrombi. At diagnosis, 19 (83%) patients were symptomatic: edema (17), pain (14), shortness of breath (2), erythema (1), and jugular venous distention (1).

Fourteen of 23 patients (61%) had an underlying diagnosis of malignancy: acute lymphoblastic leukemia (9), medulloblastoma (1), non-Hodgkin lymphoma (1), rhabdomyosarcoma (1), neuroblastoma (1), and osteosarcoma (1). In 6 patients, infectious pathogens were identified as thrombosis developed: methicillin-resistant *Staphylococcus aureus* (2), coagulase-negative *Staphylococcus* species (2), herpes simplex virus (1) and Parainfluenza 3 virus (1). One additional patient (#19) had necrotizing pneumonia, but no pathogen was identified. No patient showed any evidence of septic embolization during tPA therapy. Prothrombotic laboratory abnormalities were found in 1/5 patients with a completed testing panel (#12 lupus anticoagulant; #3, 10, 11, 17 negative), and in 8/12 with partial testing. Six of 23 patients had no testing documented. All identified protein C, protein S, or antithrombin deficiencies occurred in patients with malignancy and were acquired.

No patient had a contraindication to tPA use. Low-dose systemic tPA was initiated at 0.03–0.06 mg/kg/hr in all patients for a median of 24 hr (range 12–48 hr) (Table 2). The reasons for starting 5 patients at <0.06 mg/kg/hr tPA were not documented. Twenty-two (96%) patients received simultaneous heparin therapy (4 unfractionated, 18 LMWH) adjusted to therapeutic levels. Eight patients (#7–14) received an increased tPA dose (up to 0.12 mg/kg/hr) for an additional median of 24 hr (range 12–36 hr). tPA dose was not increased in 2 patients (#19, 20) because of major complications, in 1 patient (#16) who was subsequently treated with site-directed tPA and mechanical thrombolysis, and in 3 patients for

unidentifiable reasons. Two patients received a platelet transfusion and 1 patient received cryoprecipitate to maintain platelet count $>100 \times 10^9/L$ and fibrinogen $>100 \text{ mg/dL}$.

Response to low-dose systemic tPA therapy

Within 24 hr of thrombolytic therapy, 6 patients (#1–6) with re-imaging had an initial response to low-dose systemic tPA: 3 CR (2 oDVT) and 3 PR (3 oDVT). Continued administration of low-dose tPA in these patients led to 4 eventual CR (3 oDVT) and 2 PR (both oDVT) at the end of thrombolytic therapy (assessed at 48 hr to 1 week). tPA dose was increased to 0.12 mg/kg/hr in 8 patients (#7–14) (4 oDVT) without an initial response. At the end of thrombolytic therapy, repeat imaging revealed that 6 of these patients achieved a PR (3 oDVT). Another 6 patients (#15–20) (3 oDVT) without an initial response did not receive an increased tPA dose; none of them had a response at the end of thrombolytic therapy. Of patients treated with the lowest starting dose of tPA only for longer than 24 hr (#4–6, 16, 17, 21–23) 4/8 (50%) [4/6 (67%) oDVT] responded, but the 2 patients (#16, 17) with NR at 24 hr did not improve; of patients treated with low-dose tPA for 24 hr and then an increased dose at 24 hr due to NR (#7–14) 6/8 (75%) improved at the end of thrombolytic therapy [3/4 (75%) oDVT]. In both groups the number of CVL-related thrombi (6 and 4, respectively) and number of patients with multiple abnormal thrombophilic laboratory results (1 each) were similar. Overall response at the end of thrombolytic therapy was 13 of 22 evaluable patients (59%) [8/14 (57%) oDVT] with 4 CR (18%) [3 CR (21%) oDVT] and 9 PR (41%) [5 PR (36%) oDVT].

Further imaging in 15 patients at a median of 3 months (3 weeks to 2 years) showed a thrombus improvement rate of 93%, with 11 achieving CR and 3 PR. At their most recent imaging, 19 of 23 (83%) patients had documented thrombus improvement, with 15 achieving CR and 4 PR. Five patients received further therapy for DVT after low-dose systemic tPA: 3 had mechanical thrombectomy and 2 had site-directed tPA followed by mechanical thrombectomy. One patient also had a stent placement for the May-Thurner syndrome.

Bleeding complications

There were 2 major bleeding complications during initial low-dose systemic tPA therapy that required cessation of therapy and transfusion of blood products. One severely ill mechanically ventilated patient (#19) with pulmonary embolism and necrotizing pneumonia developed a gastrointestinal hemorrhage. Another patient (#20) developed a large femoral catheter site hematoma that extended into the retroperitoneal space. No major complications occurred when tPA dose was increased. Minor bleeding included epistaxis (2), a small hematoma at a peripheral intravenous catheter site (2), and a small hematoma at the site of recent bone-marrow aspirate (1).

DISCUSSION

This retrospective study analyzed 23 pediatric patients with acute DVT diagnosed beyond the neonatal period and treated with low-dose systemic tPA, representing the largest cohort of this type reported to date. Patients had an overall thrombolytic response rate of 59% (57% oDVT), with 18% achieving CR (21% oDVT) and 41% PR (36% oDVT) at the end of therapy. tPA dose escalation allowed 6 of 8 patients (75%) with NR at 24 hr to achieve a response at end of thrombolytic therapy (75% oDVT). These results indicate that low-dose tPA is effective in certain patients and dose escalation at 24 hr can be beneficial if there is no sufficient change in thrombus at that time.

Our study confirms the results of Wang et al.[23] that tPA dose escalation may substantially improve thrombus resolution if the initial lowest dose was not effective. A dose escalation regimen may avoid risks of bleeding for those responding to a lower dose. However, prolonged application of tPA may increase the risk of bleeding. Our results are comparable with those from another large pediatric venous thrombosis cohort treated with low-dose tPA[21], but not to other previous studies that included neonates, arterial as well as venous thrombi, higher doses of tPA, or longer treatment time.[23,24] Importantly, the present cohort was given only systemic tPA whereas other studies included catheter-directed tPA. [10,23] Our cohort included many patients with malignancy and long-term CVL. Although malignancy and treatment-related factors (steroids, asparaginase, CVL) predispose to thrombosis development, whether they directly affect response to thrombolysis is unclear. CVL-associated thrombi in our cohort may have been present in asymptomatic patients for some time before symptomatic presentation, and longer duration of thrombus could have led to a lower response rate.[26]

High doses of tPA can increase rates of serious bleeding complications in children[18–20], but this risk should decrease with lower tPA doses.[21,23,24] In our cohort, 1 patient had a gastrointestinal bleed and 1 had femoral line site hematoma, which resolved without sequelae. The latter bleeding complication may have been prevented by avoiding placing a CVL immediately before tPA. There were no additional complications with the increased tPA dose. It is unclear whether concomitant use of therapeutic anticoagulation contributed to the bleeding rate. Because of a potentially increased risk of bleeding, the 2008 ACCP guidelines recommend only concomitant prophylactic level anticoagulation.[12]

Recent ACCP guidelines also suggest that thrombolysis not be used routinely in children with DVT[12], although the rate of PTS is 10%–70%.[1,3–7,27] A pilot study of a highly selected cohort of 9 children with lower-extremity DVT and elevated prognostic biomarkers indicated that tPA-induced thrombolysis (including mechanical thrombectomy in some patients) may significantly decrease PTS development.[17] However, insufficient documentation of evaluations for PTS in our cohort prevented analysis.

The major limitations of this study are its retrospective nature and lack of control group. Anticoagulation alone might cause some response even at the 24-hr evaluation, leaving the true efficacy of the tPA regimen open to interpretation. The size of the cohort did not allow analysis of how age, underlying diagnosis, or presence of a CVL influences treatment outcome. Thrombophilic factors were incompletely studied, and a standardized interpretation approach was not used to measure outcome in imaging studies. D-dimer, a potential additional measure of tPA efficacy, was not determined. The true bleeding risk could be underrepresented by this retrospective analysis due to selection bias. Most significantly, treatment was at the physician's discretion, resulting in potential selection bias and nonuniform management, which is specifically apparent in deviations of treating partially occlusive thromboses, using lower starting doses and not administering higher doses of tPA.

In conclusion, this study indicates that low-dose systemic tPA is an effective thrombolytic agent for acute DVT in children and that dose escalation may benefit initial nonresponders but has significant limitations. Low-dose tPA may represent an intermediate treatment option between high-dose tPA and anticoagulation alone, although the risk of bleeding remains unclear. Strict guidelines for patient selection and monitoring to reduce bleeding risks based on recent studies must be followed and monitored by institutional quality assurance processes.[11,12,17,23,28,29] Cooperative prospective controlled trials can provide long-term data on the true efficacy and safety of thrombolysis as well as its influence on the development and morbidity of PTS in children.

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References

1. Monagle P, Adams M, Mahoney M, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. *Pediatr Res*. 2000; 47(6):763–766. [PubMed: 10832734]
2. Nowak-Gottl U, Junker R, Kreuz W, et al. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood*. 2001; 97(4):858–862. [PubMed: 11159508]
3. Massicotte MP, Dix D, Monagle P, et al. Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Venous Thromboembolic Complications. *J Pediatr*. 1998; 133(6):770–776. [PubMed: 9842042]
4. Kuhle S, Koloshuk B, Marzinotto V, et al. A cross-sectional study evaluating post-thrombotic syndrome in children. *Thromb Res*. 2003; 111(4–5):227–233. [PubMed: 14693168]
5. van Ommen CH, Heijboer H, van den Dool EJ, et al. Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome. *J Thromb Haemost*. 2003; 1(12):2516–2522. [PubMed: 14675086]
6. Kuhle S, Spavor M, Massicotte P, et al. Prevalence of post-thrombotic syndrome following asymptomatic thrombosis in survivors of acute lymphoblastic leukemia. *J Thromb Haemost*. 2008; 6(4):589–594. [PubMed: 18194413]
7. Sharathkumar AA, Pipe SW. Post-thrombotic Syndrome in Children: A Single Center Experience. *J Pediatr Hematol Oncol*. 2008; 30(4):261–266. [PubMed: 18391693]
8. Kahn SR. The post-thrombotic syndrome: progress and pitfalls. *Br J Haematol*. 2006; 134(4):357–365. [PubMed: 16822286]
9. Manco-Johnson MJ. Postthrombotic syndrome in children. *Acta Haematol*. 2006; 115(3–4):207–213. [PubMed: 16549898]
10. Wells PS, Forster AJ. Thrombolysis in deep vein thrombosis: is there still an indication? *Thromb Haemost*. 2001; 86(1):499–508. [PubMed: 11487040]
11. Manco-Johnson MJ. How I treat venous thrombosis in children. *Blood*. 2006; 107(1):21–29. [PubMed: 16099882]
12. Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008; 133(6 Suppl):887S–968S. [PubMed: 18574281]
13. Monagle P, Chan A, Massicotte P, et al. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004; 126(3 Suppl):645S–687S. [PubMed: 15383489]
14. Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. *Am J Med*. 1990; 88(3):235–240. [PubMed: 2106783]
15. Turpie AG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis. Results of a randomized trial. *Chest*. 1990; 97(4 Suppl):172S–175S. [PubMed: 2108855]
16. Verhaeghe R, Besse P, Bounameaux H, et al. Multicenter pilot study of the efficacy and safety of systemic rt-PA administration in the treatment of deep vein thrombosis of the lower extremities and/or pelvis. *Thromb Res*. 1989; 55(1):5–11. [PubMed: 2506661]

17. Goldenberg NA, Durham JD, Knapp-Clevenger R, et al. A thrombolytic regimen for high-risk deep venous thrombosis may substantially reduce the risk of postthrombotic syndrome in children. *Blood*. 2007; 110(1):45–53. [PubMed: 17360940]
18. Zenz W, Arlt F, Sodja S, et al. Intracerebral hemorrhage during fibrinolytic therapy in children: a review of the literature of the last thirty years. *Semin Thromb Hemost*. 1997; 23(3):321–332. [PubMed: 9255912]
19. Gupta AA, Leaker M, Andrew M, et al. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr*. 2001; 139(5):682–688. [PubMed: 11713447]
20. Leaker M, Massicotte MP, Brooker LA, et al. Thrombolytic therapy in pediatric patients: a comprehensive review of the literature. *Thromb Haemost*. 1996; 76(2):132–134. [PubMed: 8865517]
21. Knofler R, Dinger J, Kabus M, et al. Thrombolytic therapy in children--clinical experiences with recombinant tissue-plasminogen activator. *Semin Thromb Hemost*. 2001; 27(2):169–174. [PubMed: 11372772]
22. Fasano R, Kent P, Valentino L. Superior vena cava thrombus treated with low-dose, peripherally administered recombinant tissue plasminogen activator in a child: case report and review of the literature. *J Pediatr Hematol Oncol*. 2005; 27(12):692–695. [PubMed: 16344681]
23. Wang M, Hays T, Balasa V, et al. Low-dose tissue plasminogen activator thrombolysis in children. *J Pediatr Hematol Oncol*. 2003; 25(5):379–386. [PubMed: 12759624]
24. Schermer E, Streif W, Genser N, et al. Thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) in 13 children: a case series. *Wien Klin Wochenschr*. 2000; 112(21):927–933. [PubMed: 11144008]
25. Monagle P, Michelson AD, Bovill E, et al. Antithrombotic therapy in children. *Chest*. 2001; 119(1 Suppl):344S–370S. [PubMed: 11157659]
26. Manco-Johnson MJ, Nuss R, Hays T, et al. Combined thrombolytic and anticoagulant therapy for venous thrombosis in children. *J Pediatr*. 2000; 136(4):446–453. [PubMed: 10753241]
27. Kreuz W, Stoll M, Junker R, et al. Familial elevated factor VIII in children with symptomatic venous thrombosis and post-thrombotic syndrome: results of a multicenter study. *Arterioscler Thromb Vasc Biol*. 2006; 26(8):1901–1906. [PubMed: 16709943]
28. Schneppenheim R, Greiner J. Thrombosis in infants and children. *Hematology Am Soc Hematol Educ Program*. 2006:86–96. [PubMed: 17124045]
29. Raffini L. Thrombolysis for intravascular thrombosis in neonates and children. *Curr Opin Pediatr*. 2009; 21:9–14. [PubMed: 19242237]

Table 1

Patient characteristics.

Patient	Age/Sex	Underlying diagnosis	Pro-thrombotic tendencies	Thrombus at line site?	Involved venous segments	Degree of occlusion	Symptoms
1	15 F	malignancy	no	no	R external to common iliac	Occlusive	Swelling, pain
2	19 M	malignancy/bone marrow transplant	protein S	yes	R innominate	Partially occlusive	CVL malfunction
3	0.5 F	situs inversus, short gut syndrome, infection	no	yes	R subclavian, innominate, SVC	Occlusive	None
4	17 M	congenital absence of the IVC	Factor V Leiden	n/a	L superficial femoral	Occlusive	Swelling, pain, erythema
5	9 M	malignancy, paralysis	no eval	yes	R common femoral	Occlusive	Swelling
6	12 F	malignancy	protein C	yes	R brachial, axillary, subclavian	Occlusive	Swelling, pain
7	13 F	May-Thurner Syndrome	Factor V Leiden, prothrombin P20210G	n/a	L popliteal to common iliac	Occlusive	Swelling, pain
8	3 M	malignancy	no eval	yes	R cephalic, subclavian	Occlusive	Swelling, pain
9	2 M	malignancy, infection	no eval	yes	R atrial	N/A	CVL dysfunction
10	1 M	diabetes mellitus with ketoacidosis	no	yes	R common femoral to common iliac	Occlusive	Swelling, pain
11	3 F	malignancy	no	no	L common femoral to iliac	Occlusive	Swelling, pain
12	12 F	autoimmune disease	lupus anticoagulant	n/a	L proximal superficial femoral	Partially occlusive	Swelling, pain
13	1 F	malignancy	no	no	L popliteal to external iliac	Partially occlusive	Swelling, pain
14	7 M	malignancy, history of sagittal sinus thrombosis	lipoprotein a	yes	R atrial	N/A	None
15	16 M	malignancy	protein C, protein S, antithrombin III	yes	R brachial, axillary	Occlusive	Swelling, pain
16	21 F	malignancy, infection	Factor V Leiden, antithrombin III	yes	R axillary, subclavian, innominate	Partially occlusive	Swelling, pain, jugular venous extension
17	16 M	infection	no	n/a	R popliteal, superficial femoral	Occlusive	Swelling, pain
18	14 F	malignancy	protein C, antithrombin III	yes	SVC, PE	Partially occlusive	Respiratory distress
19	12 M	malignancy, infection	no eval	yes	L brachial, axillary, subclavian, PE	Occlusive	Respiratory distress
20	12 M	infection	no	n/a	L popliteal	Partially occlusive	Swelling, pain
21	7 F	malignancy	no eval	yes	R brachial, axillary, subclavian	Partially occlusive	Swelling, pain
22	10 F	Rosai-Dorfmann Syndrome	no	yes	SVC	Occlusive	Swelling
23	2 M	severe hemophilia A, infection	no eval	yes	L and R subclavian, innominate	L occlusive	Swelling

Patient	Age/Sex	Underlying diagnosis	Pro-thrombotic tendencies	Thrombus at line site?	Involved venous segments	Degree of occlusion	Symptoms
R partially occlusive							

IVC inferior vena cava; n/a not applicable due to no central venous line; R right; L left; SVC superior vena cava; PE pulmonary embolism; CVL central venous line.

Table 2

Patient treatment and outcomes.

Patient	Starting dose (mg/kg/hr)/ Duration of starting dose (hr)	Thrombus resolution at 24 hours	Increased dose (mg/kg/hr)/ Duration of increased dose (hr)	Thrombus resolution at end of thrombolytic therapy	Post-therapy evaluation/Time from therapy
1	0.06/24	CR	n/a	CR	no eval
2	0.05/16	CR	n/a	CR	no eval
3	0.03/12	CR	n/a	CR	no eval
4	0.03/40	PR	n/a	PR	CR/3 months
5	0.06/48	PR	n/a	PR	CR/2 months
6	0.06/26	PR	n/a	CR	no eval
7	0.06/12	NR	0.11/12 [‡]	NR	CR/3 months
8	0.06/16	NR	0.12/32	PR	CR/3 weeks
9	0.06/24	NR	0.12/24	PR	CR/3 months
10	0.06/12	NR	0.12/28 [‡]	PR	CR/3 months
11	0.06/23	NR	0.12/24	PR	CR/6 weeks
12	0.06/37	NR	0.12/19	PR	CR/3 months
13	0.06/22	NR	0.12/36	PR	no eval
14	0.06/27	NR	0.12/15	NR	CR/3 weeks
15	0.06/22	NR	n/a	NR	PR/6 weeks
16	0.06/48	NR	n/a [‡]	NR	PR/2 years
17	0.03/48	NR	n/a	NR	PR/3 months
18	0.05/24	NR	n/a	NR	no eval
19	0.06/12 [§]	NR	n/a	NR	no eval
20	0.06/34 [§]	NR	n/a	no eval	NR/6 months
21	0.06/38	no eval	n/a	PR	CR/6 weeks
22	0.06/37	no eval	n/a [‡]	NR	CR/6 months
23	0.06/48	no eval	n/a [‡]	NR	no eval

[§] major complication; further treatment:[‡] site-directed thrombolysis.

‡ mechanical thrombectomy; n/a not applicable due to no dose escalation; PR partial resolution of thrombus, NR no change in thrombus imaging.