Thrombosis Research 133 (2014) 364–370

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Post-marketing surveillance of thrombomodulin alfa, a novel treatment of disseminated intravascular coagulation - Safety and efficacy in 1,032 patients with hematologic malignancy

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ARTICLE INFO

Article history:
Received 21 June 2013
Received in revised form 28 November 2013
Accepted 28 December 2013
Available online 4 January 2014

Keywords:
Disseminated intravascular coagulation
Hematologic malignancy
Post-marketing surveillance
Thrombomodulin

ABSTRACT

Introduction: Post-marketing surveillance of thrombomodulin alfa (TM-α) was performed to evaluate safety and efficacy in patients with disseminated intravascular coagulation (DIC) with hematologic malignancy.
Materials and methods: All patients treated with TM-α from May 2008 to April 2010 in Japan were included. Information about baseline characteristics, safety, and efficacy were collected. The DIC resolution rate, survival rate on Day 28 after the last TM-α administration, and changes in DIC score and coagulation tests were evaluated.
Results: The underlying diseases associated with DIC were acute myeloid leukemia (except for acute promyelocytic leukemia, n = 350), lymphoma (n = 199), acute promyelocytic leukemia (n = 172), acute lymphoblastic leukemia (n = 156), myelodysplastic syndromes (n = 61), and other (n = 94). The incidence rates of bleeding-related adverse events and adverse drug reactions were 17.8% and 4.6%, respectively. In subjects with bleeding symptoms at baseline, 55.0% were assessed as disappeared or improved based on symptoms after TM-α treatment. The DIC resolution and survival rates were 55.9% and 70.7%, respectively. The DIC score and coagulation tests including thrombin-antithrombin complex (TAT) were significantly improved. Coagulation tests were significantly improved after TM-α treatment even in subjects whose clinical course of underlying disease was assessed as unchanged or exacerbated.
Conclusions: This surveillance confirmed the safety and efficacy of TM-α in clinical practice, thus TM-α may be an ideal treatment for patients with DIC based upon hematologic malignancy.

Introduction

Disseminated intravascular coagulation (DIC) is frequently found in patients with severe sepsis, hematologic malignancy, solid tumor, and trauma [1–3]. In such patients, excessive activation of coagulation results in fibrin deposition in systemic microvessels.

The causes of DIC associated with hematologic malignancy are considered to be an elevated expression of tissue factor, tissue-type plasminogen activator, or annexin II in leukemia cells [4–8]. It is important to aggressively treat the underlying disease associated with DIC. However, it is often impossible to swiftly address triggering events for DIC such as bleeding symptoms. Based on the notion that DIC is primarily characterized by extensive activation of coagulation, anticoagulant treatment is recommended in several guidelines as the rational

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; APL, acute promyelocytic leukemia; APTT, activated partial thromboplastin time; AT, antithrombin; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DIC, disseminated intravascular coagulation; FDP, fibrin and fibrinogen degradation products; JMHW, Japanese Ministry of Health and Welfare; JMHLW, Japan Ministry of Health, Labour, and Welfare; LDH, lactate dehydrogenase; MDS, myelodysplastic syndromes; MM, multiple myeloma; PIC, plasmin α2-plasmin inhibitor complex; PT, prothrombin time; SAE, serious adverse event; SPI, serine protease inhibitor; TAT, thrombin-antithrombin complex; TM, thrombomodulin; WBC, white blood cell.

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http://dx.doi.org/10.1016/j.thromres.2013.12.033

approach for DIC [9,10]. However, no anticoagulants with evidence-based, high-grade recommendations in the treatment of DIC are associated with hematologic malignancy.

Thrombomodulin (TM) is a thrombin receptor on the endothelial cell surface that plays an important role in the regulation of intravascular coagulation [11,12]. TM binds to thrombin to inactivate coagulation and the thrombin-TM complex activates protein C to form activated protein C, which cleaves and inactivates factors Va and VIIIa in the presence of protein S. As a result, TM acts as a negative feedback regulator according to the amount of excessively generated thrombin. TM additionally supports thrombin-mediated activation of thrombin activatable fibrinolysis inhibitor (TAFI), which has antifibrinolytic properties [13,14]. Moreover, TM regulates inflammation through its N-terminal lectin-like domain [15–17]. Thrombomodulin alfa (TM-α) is a recombinant human soluble TM possessing an extracellular domain that includes an active site. The effects of TM-α on DIC were previously examined in a multicenter, randomized, clinical trial in Japan [18]. In patients whose DIC was associated with hematologic malignancy, resolution of DIC and the disappearance rate of bleeding symptoms were significantly better in the TM-α group than in the heparin group. TM-α was approved for the indication of DIC in 2008 in Japan. After the commercial launch, the clinical use survey was conducted by continuous registration, where all cases using TM-α were registered until the target number was reached (infection, hematologic malignancy: ≥1,000 cases, total: ≥3,000 cases) [19]. We report the safety and efficacy of TM-α treatment focusing on patients with DIC whose underlying disease was hematologic malignancy.

Materials and Methods

Design and Data Collection

Patients were consecutively registered at the initiation of TM-α treatment and prospectively monitored during observation periods. At the start of TM-α administration, information about the following patient characteristics was collected: age, gender, severity of underlying disease, duration of DIC, DIC treatment at baseline, type of complications (renal impairment, hepatic impairment, other), bleeding symptoms, and organ symptoms. The standard dose of TM-α was 380 U/kg/day, which was the same as the dose in phase 3 (0.06 mg/kg/day) [18,20]. The adjusted dose of 130 U/kg/day of TM-α was used to treat patients with renal dysfunction due to a decreased clearance rate of TM-α from the circulation of these patients [21]. No limit was placed on either the administration period of TM-α or the concomitant use of anticoagulants other than TM-α and blood preparations. The clinical course of underlying disease was assessed by the attending physicians as improved, unchanged, or exacerbated based on clinical symptoms and laboratory test results on the day after final treatment with TM-α. Fibrin and fibrinogen degradation products (FDP), platelet count, fibrinogen, prothrombin time (PT) ratio, activated partial thromboplastin time (APTT), thrombin-antithrombin complex (TAT), plasmin α2-plasmin inhibitor complex (PIC), antithrombin (AT), and other general coagulation tests were measured at each institute. Serum samples collected at baseline and on Day 28 after the last TM-α administration were tested for antibodies against TM-α.

This surveillance was conducted in accordance with the guidelines for Good Post-Marketing Surveillance Practices as required by the Japan Ministry of Health, Labour, and Welfare (JMHLW). All patients were treated according to the attending physician's discretion and there were no limitations on the concomitant use of other anticoagulants and medication for the treatment of underlying diseases and complications. In addition, personal data anonymization was carried out upon data collection. Therefore, approval of this surveillance by ethics committees or institutional review boards and the acquisition of informed consent from patients were not deemed necessary.

Safety Evaluation

Safety data were coded with preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA/J) version 13.1 [22]. The definitions of adverse events (AEs) and adverse drug reactions (ADRs) were based on the ICH guidelines [23]. The safety evaluation included AEs observed until the day after the last TM-α administration and all ADRs and serious AEs (SAEs) observed until Day 28 after the last TM-α administration.

Efficacy Evaluation

The DIC resolution rate was calculated using the DIC score, which was based on the diagnostic criteria of the Japanese Ministry of Health and Welfare (JMHW) [24]. The JMHW criteria that were used in our study have two scoring systems - patients with or without severe thrombocytopenia [24]. In this study, we analyzed the DIC resolution rate in the group of subjects with severe thrombocytopenia due to bone marrow failure. Subjects with severe thrombocytopenia due to bone marrow failure were evaluated; resolution of DIC was defined as a score of ≤2 points. The survival rate was calculated based on the number of subjects who were alive on Day 28 after the last TM-α administration. Coagulation test items related to coagulation/fibrinolysis in DIC were measured at baseline, during the administration period, and on the day after the last administration. The clinical course of bleeding symptoms was assessed as previously described [18]. In brief, the severity of symptoms was evaluated in 4 grades (+++, ++, +, −) based on the evaluation criteria established for each symptom. Changes in the grade of each symptom from the start of TM-α administration to the day after the last administration were collectively evaluated on a scale of (i) to (iv): (i) disappeared (all symptoms disappeared); (ii) improved (total number of improved symptoms was higher than that of exacerbated or new symptoms); (iii) unchanged (the only confirmed symptom remained unchanged, or total number of improved symptoms was comparable to that of exacerbated or new symptoms); (iv) exacerbated (total number of improved symptoms was lower than that of exacerbated or new symptoms).

Data Analysis

A multivariate analysis was performed to identify the risk factors affecting the development of bleeding-related AEs and ADRs. The 14 baseline characteristics used in the analysis were age, gender, severity of underlying disease, medical history related to the risk of bleeding, duration of DIC, renal function (creatinine clearance classification) [25], hepatic impairment, bleeding symptoms at baseline, organ symptoms at baseline, platelet counts, FDP, fibrinogen, AT, and PT ratio.

Intergroup comparisons were performed by the chi-square test. Changes in the DIC score and coagulation tests from baseline to the day after the last administration were examined using the Wilcoxon signed-rank test. Statistical significance was determined with a 2-sided p value < 0.05. Statistical testing was performed with JMP version 8.0 (SAS Institute Co. Ltd., Cary, NC).

Results

Subject Demographics

A total of 1,121 patients with DIC whose underlying disease was a hematologic malignancy were included in this survey. Of these, 1,032 had never been treated with TM-α. Unless otherwise specified, safety and efficacy were analyzed in the 1,032 subjects treated with TM-α for the first time. The baseline characteristics of these 1,032 subjects are shown by underlying disease in Table 1. The underlying diseases associated with DIC were acute myeloid leukemia (except for acute promyelocytic leukemia) (AML, 33.9%), lymphoma (19.3%),