Hypothesis

Multidrug Treatment Using Kampo Medicine for Severe Fever with Thrombocytopenia Syndrome

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Multidrug Treatment Using Kampo Medicine for Severe Fever with Thrombocytopenia Syndrome

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Abstract

Severe fever with thrombocytopenia syndrome virus (SFTSV) is an emerging tick-borne bunyavirus that causes acute febrile illness characterized by thrombocytopenia and a high mortality rate. Currently, no specific antiviral drugs have been approved for the treatment of SFTSV; therefore, identifying effective drugs against the disease and conducting clinical trials of these drugs are crucial. Drug repurposing is a well-established strategy for utilizing existing licensed drugs for newer indications, facilitating the shortest possible transition from bench to bedside. This approach demonstrated that favipiravir, zaltoprofen, ivermectin, and lurasidone, along with the phytochemicals licoflavone C and oleanolic acid, are efficacious against the SFTSV. Glycyrrhiza, which contains licoflavone C in its extracts, is a component of the Kampo medicines Kakkon-to, Shosaiko-to and Saiko-keishi-to. Ginseng, which contains oleanolic acid in its extracts, is a component of Shosaiko-to and Saiko-keishi-to. Kampo medicine is a traditional Japanese medicine primarily consisting of organic plant-based ingredients, such as Glycyrrhiza, Ginseng, and others. Multidrug treatment is effective due to the synergistic effects resulting from the various mechanisms of action of the concerned drugs. Therefore, the combination of drugs, such as favipiravir, ivermectin, and Shosaiko-to may be more efficacious against the SFTSV.

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Severe fever with thrombocytopenia syndrome virus (SFTSV) is an emerging tick-borne bunyavirus that causes SFTS, characterized by acute febrile illness and thrombocytopenia, with a high mortality rate ranging from 16.2 to 47% in humans. SFTSV was identified in China, South Korea, and Japan in the early 2010s [1]. SFTSV belongs to the genus Bandavirus within the family Phenuiviridae and is characterized by a negative-sense, single-stranded RNA genome comprising three segments: large (L), medium (M), and small (S). The L segment encodes the RNA-dependent RNA polymerase (RdRp) involved in viral RNA replication. This enzyme is multifunctional and includes a cap-dependent endonuclease domain, which plays a critical role in viral transcription through a process called cap-snatching, wherein the host mRNAs are cleaved near their 5′ cap structures. The capped RNA fragments are subsequently used as primers by the viral RdRp to synthesize viral mRNAs [2]. The M segment encodes the envelope glycoprotein, which facilitates host cell entry and mediates virion maturation and assembly. The S segment, a small genome part, encodes a nucleoprotein (NP) that plays a pivotal role in the viral lifecycle by binding to the viral genomic RNA and forming ribonucleoprotein complexes. These complexes are crucial for viral replication and packaging.

Currently, no specific antiviral drugs, including ribavirin, have been approved for the treatment of SFTSV infection. Favipiravir, a broad-spectrum antiviral drug originally developed for influenza, is known to inhibit the activity of RdRp of various RNA viruses. A Japanese multicenter clinical trial demonstrated that favipiravir treatment reduced the fatality rate of SFTS patients by approximately

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10% compared to previously reported fatality rates from epidemiological surveys. Patients with lower viral loads at the start of treatment had significantly better outcomes [1]. Therefore, in 2024, favipiravir was officially approved as the world's first antiviral drug for SFTS. Using an in silico study, Chatterjee et al. demonstrated that zaltoprofen, a non-steroidal anti-inflammatory drug, binds to the L segment-coded L protein that functions as the SFTSV RdRp, and interferes with viral replication [3]. As a drug candidate targeting the NP, ivermectin was shown in another in silico study by Sengupta et al. to strongly interact with the NP, thereby interfering with viral replication [4]. Similarly, Cheng et al. demonstrated that lurasidone, an antipsychotic, exerts an antiviral effect by directly binding to the SFTSV NP and disrupting genome replication [5]. Regarding a cap-dependent endonuclease inhibitor against SFTSV, a high-throughput FRET-based enzymatic screening system identified licoflavone C, oleanolic acid, and 3,4-dicaffeoylquinic acid as potential candidates [6]. Glycyrrhiza, which contains licoflavone C in its extracts, is a component of the Kampo medicines (KMs) Kakkon-to, Shosaiko-to and Saiko-keishi-to. Ginseng, which contains oleanolic acid, is a component of Shosaiko-to and Saiko-keishi-to. KM is a traditional Japanese medicine primarily consisting of organic plant-based ingredients, such as Glycyrrhiza, Ginseng, Scutellaria, Ziziphus jujuba, Bupleurum, and others. Kakkon-to, Shosaiko-to and Saiko-keishi-to have been prescribed for the treatment of COVID-19 and influenza in Japan owing to their antiviral and anti-inflammatory properties [7–9]. These findings indicate that they may be also be efficacious against SFTSV. Approximately 150 types of KM can be commercially prescribed in Japan. KMs are inexpensive and routinely prescribed by clinicians in Japan for various conditions, including pulmonary diseases, hepatic diseases, urological diseases, menopausal disorders, dementia. Moreover, KMs are associated with fewer adverse reactions compared to Western medicines.

Taken together, the aforementioned drugs may be recognized as SFTSV inhibitors in the near future. Multidrug treatment is effective due to the synergistic effects of the different mechanisms of action of the involved drugs. Additionally, multidrug treatment may prevent the emergence of drug-resistant SFTSV. Therefore, a combination of drugs, such as favipiravir, ivermectin, and Shosaiko-to, may be more efficacious against SFTSV. Nonetheless, clinical trials are warranted to better assess the optimal doses and durations, as well as the efficacy and tolerability of this combination before its clinical application.

Conflicts of interest: The authors have no conflict of interest associated with this article.

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