Influence of Selective Serotonin Reuptake Inhibitors on Bleeding Risk in Patients with Severe Thrombocytopenia after Chemotherapy: A Retrospective Study

Claudia Schäfer  Alix O’Meara  Dimitrios A. Tsakiris  Michael Medinger
Jakob R. Passweg  Martin Stern
Division of Hematology, University Hospital Basel, Basel, Switzerland

Several in vivo and in vitro studies have indicated that selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding [1–6]. The highest risk of hemostatic complications has been documented for patients treated concurrently with drugs interfering with plasmatic hemostasis or with platelet function (e.g., oral anticoagulation and nonsteroidal anti-inflammatory drugs) and for gastrointestinal bleeding as an endpoint. In contrast, other studies have failed to detect an association between SSRI treatment and a higher risk of bleeding [7–9].

Clinically relevant bleeding due to iatrogenic thrombocytopenia is one of the main complications of high-dose chemotherapy used in the treatment of leukemia [10]. To date, no studies have analyzed whether administration of SSRIs is safe in terms of bleeding risk in such a population at a highly elevated risk for bleeding [11].

To assess the bleeding risk, we analyzed a cohort of 300 patients with severe iatrogenic thrombocytopenia undergoing high-dose chemotherapy for acute or chronic leukemia (n = 100) or myeloablative conditioning chemotherapy followed by autologous (n = 100) or allogeneic (n = 100) hematopoietic stem cell transplantation (HSCT). Data were collected from charts of consecutive patients treated at the Division of Hematology at Basel University Hospital. Data were analyzed from the start of chemotherapy, or in case of HSCT from the day of the allogeneic or autologous HSCT until discharge. During treatment, clinical examination and laboratory tests were performed every day. For bleeding prophylaxis, irradiated thrombocyte concentrates collected by single donor apheresis were given at a thrombocyte count of <30 × 10⁹/l when treated with low-molecular-weight heparin (LMWH), <20 × 10⁹/l in patients with fever or graft-versus-host disease, or when the morning platelet count was <10 × 10⁹/l. Patients with a developing thrombosis received LMWH as a 24-hour infusion with a target anti-FXa level of 0.2–0.4 IE/ml (measured daily), and LMWH infusion was immediately stopped when a bleeding event scored ≥ 3 occurred. Veno-occlusive disease prophylaxis with unfractionated heparin was given to patients treated with allogeneic HSCT after myeloablative conditioning with a dose of 5,000 units per day as a continuous infusion until engraftment. All protocols were approved by the ethics committee and all patients gave informed consent to their treatment and to having their data analyzed.

Antidepressant drugs were categorized as SSRIs or non-SSRIs. The dose of antidepressants administered was not considered. The bleeding events were graduated using the ITP bleeding score from 0 (no hemorrhage), 1
(minor bleeding, e.g. few petechiae), 2 (mild bleeding with many petechiae and bruises, but without mucosal bleeding), 3 (moderate bleeding including mucosal, not requiring intervention), 4 (severe bleeding including internal hemorrhage, requiring intervention), and 5 (life-threatening or fatal bleeding) [12].

The effect of SSRI administration on bleeding risk was estimated using incidence rates (bleeding events per in-hospital day undergoing or not undergoing SSRI/non-SSRI treatment) and multivariable Cox models. Incidence rates were compared using Pearson’s χ² test. In Cox models, SSRI and non-SSRI use was modeled as a time-dependent covariable, i.e. the effect of drug administration was estimated in patients on treatment versus those not receiving SSRIs or non-SSRIs. Estimates were adjusted for factors known to influence the bleeding risk: thrombocyte count, inflammation (modeled by C-reactive protein), azotemia (modeled by blood urea nitrogen), treatment with LMWH, and the presence of graft-versus-host disease after allogeneic HSCT [11]. All covariables were measured or graded daily during hospitalization and considered in the analysis. Non-time-dependent factors such as type of treatment (chemotherapy vs. autologous vs. allogeneic HSCT) were also included. All p values were 2-sided and were considered significant if <0.05. All statistical analyses were performed using STATA 12 (StataCorp LP, College Station, Tex., USA).

In our cohort, the median age was 50 years (range: 18–80). 158 patients were treated for acute myeloid leukemia or myelodysplastic syndrome, 23 for acute lymphoblastic leukemia, 56 for multiple myeloma, 40 for lymphoproliferative disorders, 9 for chronic myeloid leukemia, and 14 for other diseases. Median duration of in-hospital treatment was 24 days (range: 5–66) for a total of 7,521 patient days. The majority of patients (256/300, 85%) received one or more platelet transfusions. Of the 300 patients, 75 (25%) were treated with an antidepressant (SSRIs n = 43, non-SSRIs n = 22, or both n = 10). The mean duration of antidepressant treatment during the inpatient period in this study was 16 days (range: 2–39) for SSRIs and 23 days (range: 3–66) for non-SSRIs. On a total of 834 patient days (11% of all days), patients were under treatment with an SSRI, and on 687 patient days (9% of all days), patients were under treatment with a non-SSRI. In the SSRI group, the administered drugs were (es)citalopram (given to 48 patients) and sertraline (given to 5 patients). From the non-SSRI group, mirtazapine was given to 17 patients, venlaflaxine to 8 patients, trimipramine to 6 patients, and the remaining antidepressants once (amitriptyline, clomipramine, mianserin, and trazodone).

Bleeding events of a lower degree such as petechiae occur frequently, but without a major impact on prognosis. We therefore analyzed all grades of bleeding (grades 1–5), as well as the more clinically meaningful moderate to severe bleeding events (grades 3–5). In this patient population, a total of 187 bleeding events were recorded in 123 patients (95 grade 1, 30 grade 2, 40 grade 3, 15 grade 4, 9 grade 5; fig. 1a). The cumulative incidences of grade 1–5 and grade 3–5 bleeding at day 50 after the start of treatment were 41 ± 3% and 17 ± 2%, respectively (fig. 1b). Twenty-three bleeding events (12% of all events: 13 grade 1, 5 grade 2, 3 grade 3, 2 grade 4, and 0 grade 5) occurred during SSRI treatment. Twenty bleeding events (11% of all events: 10 grade 1, 4 grade 2, 3 grade 3, 3 grade 4, and 0 grade 5) occurred during non-SSRI treatment. Crude incidence rates per day of in-hospital days showed no increased rate of bleeding of any grade in patients on treatment with SSRIs or non-SSRIs, when compared to patients not undergoing such treatment (fig. 2). Important-
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In multivariable adjusted Cox regression analyses, we found no elevated risk for bleeding in patients undergoing SSRI or non-SSRI treatment, either for bleeding of any grade or for bleeding of grades 3–5 [hazard ratio (HR) for SSRIs for bleeding grade 1–5: 0.98, 95% CI: 0.63–1.37, p = 0.92; HR for SSRIs for grade 3–5 bleeding: 0.48, 95% CI: 0.17–1.37, p = 0.17; HR for non-SSRIs for bleeding grade 1–5: 0.94, 95% CI: 0.64–1.40, p = 0.77; HR for non-SSRIs for grade 3–5 bleeding: 1.11, 95% CI: 0.52–2.36, p = 0.78]. Interaction analysis assessed if the HRs for SSRIs or non-SSRIs regarding bleeding risk were modulated by platelet counts, and found no significant interaction (p = 0.72 for SSRIs, p = 0.88 for non-SSRIs), suggesting that both types of antidepressants do not increase the risk for bleeding even in patients with very low platelet counts. Similarly, no significant interaction on bleeding risk was found in patients treated with an SSRI or a non-SSRI and concurrent LMWH application (p = 0.97 and p = 0.94, respectively). Thirty bleeding events (16% of all events) occurred in the gastrointestinal tract. Similar to the overall risk, neither SSRI nor non-SSRI treatment significantly increased the risk for gastrointestinal bleeding (HR for SSRIs: 0.97, 95% CI: 0.28–3.30, p = 0.96; HR for non-SSRIs: 1.48, 95% CI: 0.67–3.23, p = 0.33).

In conclusion, we could not detect an effect of SSRI or non-SSRI treatment on bleeding events in patients with severe thrombocytopenia induced by chemotherapy. SSRIs [e.g. (es)citalopram] and non-SSRIs (such as mirtazapine) may be safely used in patients with severe thrombocytopenia.

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Fig. 2. Incidence rates (per day of in-hospital treatment) of bleeding events graded by the ITP bleeding score in patients not undergoing antidepressant treatment (no AD), and in patients with SSRI or non-SSRI treatment.

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