Outpatient Management of Patients with Immune Thrombocytopenia (ITP) by Hematologists 1995–2014

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Introduction

Immune thrombocytopenia (ITP) is an autoimmune-mediated reduction in platelet numbers due to autoantibodies against platelets and megakaryocytes. Dysregulation of B- and T-regulatory cells leads to impaired platelet production in the bone marrow and to a relative reduction in thrombopoietin (TPO) levels [1–5]. In most cases, ITP is diagnosed because of mild bleeding symptoms such as petechial and mucous membrane hemorrhages being the most frequent. Rarely major intracranial or gastrointestinal hemorrhages or menorrhagia occur as the first bleeding complications in ITP. Frequent routine blood analyses by general practitioners lead to the detection of mild ITP without bleeding symptoms. The incidence is estimated to be 1.6–3.95/100,000/year and the prevalence 9.5–20/100,000/year [6, 7]. In a patient who feels otherwise well and has an unremarkable physical examination and normal hemoglobin and leukocyte levels, primary and secondary ITP have to be discriminated [8]. Especially secondary ITP due to indolent B-cell lymphomas, autoimmune diseases, human immunodeficiency virus, and hepatitis B and C have to be excluded [8]. Newly diagnosed, persistent, and chronic ITP have to be discriminated due to the high spontaneous remission rate of newly diagnosed ITP with different treatment approaches [8, 9]. The goal of therapy in ITP is to prevent bleeding. The current guidelines of the American Society of Hematology (ASH) suggest to start treatment as soon as platelets are below 20–30 G/l or bleeding occurs, although the authors emphasize that there is little evidence to support a certain platelet number as the sole trigger for therapy [10]. The current German-Austrian-Swiss guidelines suggest that therapy should start as soon as clinically relevant bleeding occurs according to World Health Organization (WHO) criteria [9]. Patients without any bleeding symptoms should not be treated due to lacking evidence of benefit and the very low likelihood of serious hemorrhages [9]. Whether to start...
treatment in a patient who is not bleeding should always be jointly decided by the patient and the hematologist [9]. Approved treatment modalities most frequently used and recommended are steroids, intravenous immunoglobulins (IVIG), splenectomy, thrombopoietin receptor agonists (TRAs), and other immunosuppressive agents (OISA) like azathioprine. Although rituximab has shown activity in ITP, it is not approved for treatment of ITP [9, 10].

In Germany, many patients with ITP are still being diagnosed and treated in hospitals. During the last 25 years, more than 600 office-based hematologists have set up community-based independent practices to diagnose and treat patients close to home [11]. To the best of our knowledge, no data are available on how office-based hematologists diagnose and treat outpatients with ITP in routine care. We therefore carried out a retrospective study in outpatients with ITP focusing on the following key questions: i) How are patients diagnosed and treated?; ii) Which therapy sequences are applied?; iii) How successful is the treatment?; iv) How many patients die due to bleeding complications?; and v) How many patients need hospital treatment for ITP?

Patients and Methods

This was a retrospective analysis of all patients with ITP who were seen by 5 hematologists at the Praxisklinik für Hämatologie und Onkologie in Koblenz between 06/1995 and 12/2014. Data were extracted from patient files into a database and were statistically analyzed using SPSS 19 (IBM Corp., Armonk, NY, USA). All patients gave written informed consent for data analysis and data publication.

At the initial diagnosis, the following data (among others) were collected: sex, age, platelet number, diagnostic workup, stage and classification, and comorbidities. In the course of the disease, the following was captured: therapies, changes in therapy regimens, responses to treatment, hospitalizations, and survival. For classification of ITP and therapy response criteria, current guidelines and working group criteria were used accordingly [9, 10, 12]. The Charlson comorbidity index [13], assigning a weighted score to each comorbid condition based on the relative risk of 1-year mortality, was used to classify comorbidities. Statistical analyses were descriptive, specific hypotheses were not tested. Frequencies and statistical measures of central tendency were calculated, and a survival analysis was performed according to the method of Kaplan-Meier.

Results

Patients

A total of 422 patients were diagnosed with ITP during the evaluation period. 57% were female and 43% male. The median age was 55 years (range 7–91 years). 89% of patients suffered from primary ITP and 76% from chronic ITP according to working group criteria [12]. The median platelet number at the time of diagnosis was 59 G/l (range 0–148 G/l). 63% of patients had comorbidities which were mostly cardiovascular and metabolic. The median Charlson score was 0 (range 0–6). Patient characteristics are shown in table 1.

Bone Marrow Biopsy

In 57% of patients, a bone marrow biopsy was performed. There was a difference in the frequency of bone marrow biopsies according to the time period of diagnosis (72% in 2004 and earlier vs. 44% after 2004).

Treatment

A total of 47% of patients received some form of therapy. 52% of the female patients received therapy compared to 40% of the male patients. The median platelet count at the time of first treatment was 17.5 G/l (range 0–101 G/l). There was a difference between the platelet count at first treatment according to the time period of diagnosis (19 G/l (range 0–101 G/l) in 2004 and earlier vs. 15 G/l (range 0–86 G/l) after 2004). Patients received a median of 2 treatment lines (range 1–10). The most frequently used treatment modalities were steroids in 93%, IVIG in 55%, splenectomy in 21%, and OISA in 23% of patients. Rituximab and TRAs were used in 10% and 6% only. First-line therapy (n = 198) consisted of steroids in 81%, IVIG in 12%, and IVIG plus steroids in 6%. Second-line therapy (n = 105) consisted of IVIG in 48%, IVIG plus steroids in 18%, steroids in 23%, OISA in 11%, and splenectomy in 5%. Third-line therapy (n = 68) consisted of OISA in 34%, splenectomy in 21%, IVIG in 15%, rituximab in 9%, IVIG plus steroids in 9%, steroids in 25%, and TRAs in 4%. Fourth-line therapy (n = 40) consisted of OISA in 38%, splenectomy in 25%, IVIG in 15%, rituximab in 10%, IVIG plus steroids in 8%, steroids in 25%, and TRAs in 3%. OISA included in the order of frequency mycopheno-
late mofetil, azathioprine, cyclophosphamide, cyclosporine A, chloroquine, and methotrexate. OISA were often used in combination with steroids. The sequential therapy is depicted in figure 1.

**Response**

The treatment modalities most frequently used were steroids in 93%, IVIG in 55%, splenectomy in 21%, and OISA in 23% of patients. Rituximab and TRAs were used in 10% and 6% only. Responses (complete response (CR) and partial response (PR)) to steroids were seen in 57%, to IVIG in 47%, to splenectomy in 71%, to OISA in 44%, to rituximab in 48%, and to TRAs in 53%. After the last therapy, 72% of all patients showed a CR or PR, 10% had no response, and 18% were lost to follow-up or response was not evaluable. 73% were off treatment, 14% were on treatment, and 13% were lost to follow-up.

**Hospitalization**

A total of 161 (38%) patients had to be hospitalized at some point after the initial diagnosis. Hospitalizations occurred most frequently for comorbidities (55%). Only 2% of patients needed to be hospitalized due to bleeding complications.

**Death**

At the end of the evaluation period, 68% of patients are alive, 24% are lost to follow-up, and 34 (8%) patients have died. Of the patients who died, only 1 (0.2%) died due to a fatal hemorrhage. This was a 68-year-old lady with refractory chronic lymphocytic leukemia which had transformed into a secondary high-grade B-cell lymphoma and secondary ITP. She died in 2002 of a cerebral hemorrhage.

**Discussion**

The ASH 2011 ITP guidelines suggest treatment if platelets are below 30 G/l [10]. In any case of platelets below 30 G/l without bleeding, advantages and disadvantages of therapy have to be discussed with the patient and shared decision making is important. The current German-Austrian-Swiss ITP treatment guidelines suggest starting therapy as soon as the patient is bleeding rather than below a certain platelet threshold [9]. If bleeding is evident, hospital admission is advised [9]. First-line therapy should consist of steroids, and additional IVIG should be given if severe bleeding (WHO grade II–IV) is present [9]. Platelet transfusions can be given in the case of life-threatening bleeding episodes [9, 10]. As second-line therapy, splenectomy should be offered [9, 10]. As an alternative, TRAs can be used if contraindications to splenectomy exist or the patient refuses the procedure. The cornerstone of third-line therapy after splenectomy are TRAs (romiplostim or eltrombopag) [14]. If TRAs are not effective or not tolerated by the patient, OISA like azathioprine, cyclophosphamide, cyclosporine A, mycophenolate mofetil, or rituximab are further treatment options [9]. Treatment and outcome data of our patient cohort shows that the majority of ITP patients can be managed as outpatients by experienced hematologists thus reducing treatment costs and the rate of hospital-acquired infections and improving the patients’ quality of life. Only 9 (2%) patients needed hospital-based therapy due to serious bleeding complications. The treatment modalities most frequently used were steroids in 93%, IVIG in 55%, splenectomy in 21%, and OISA in 23% of patients. Rituximab and TRAs were used in 10% and 6% only. The fact that during first-line therapy every patient received steroids and/or IVIG proofs that current therapy guidelines are followed by the hematologists at this institution [9]. 55% of patients received IVIG, and 38% of these needed no further therapy thereafter. 21% of patients were offered and accepted splenectomy. 71% of these no longer required treatment after splenectomy. 23% of the patients who refused splenectomy or relapsed after splenectomy were treated with OISA. In 56%, this treatment was successful, 44% needed further therapies. The low application rate of TRAs is due to the fact that romiplostim and eltrombopag were approved for patients after splenectomy in Germany as late as 2009/2010. This also explains the relatively high proportion of patients treated with OISA (23%). 72% of patients achieved a durable remission (complete or partial) after their last therapy. 145 (73%) patients are off treatment. 1 (0.2%) patient died due to bleeding complications. This is in line with other studies reporting a low rate of serious life-threatening bleeding complications in ITP [15, 16]. Interesting to us was our own learning curve concerning bone.
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marrow biopsies as part of the diagnostic process. We observed a decline in frequency in relation to the time of first ITP diagnosis (72% in 2004 and earlier vs. 44% thereafter). Another obvious difference concerned the platelet count at first therapy, which was lower in recent years (19 G/L in 2004 and earlier vs. 15 G/L thereafter). The strengths of our evaluation are that it reflects routine care diagnostic procedures and therapy, that all patients with ITP were analyzed, and the long evaluation period. Weaknesses are the monocentric situation and the incompleteness of the data concerning follow-up due to the retrospective character.

In summary, the results of our retrospective analysis suggest that the majority of patients with ITP can be managed safely as outpatients by experienced hematologists. Treatment according to national and international guidelines in routine care leads to a high percentage of patients who no longer require therapy. Hospitalization rates and mortality due to bleeding are low in ITP patients who are cared for on an outpatient basis.

Disclosure Statement

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References


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