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Dasatinib, large granular lymphocytosis, and pleural effusion: Useful or adverse effect?

Semra Paydas *

Cukurova University, Faculty of Medicine, Department of Oncology, Adana, Turkey

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Contents

Abstract

Dasatinib is a second generation tyrosine kinase inhibitor approved for clinical use in first line and imatinib-resistant chronic myeloid leukemia and Philadelphia positive (Ph+) acute lymphoblastic leukemia. In addition to BCR-ABL1, dasatinib inhibits TEC kinases and SRC family kinases and is more potent than imatinib in the treatment of Ph+ leukemias. In the last 3 years, increases in cytotoxic T and natural-killer cells in peripheral blood samples have been reported in cases treated by dasatinib. The awareness of the clonal expansion of large granular lymphocytes and beneficial effect of these clonal cells increased the interest to dasatinib in cases receiving this drug. Clonal expansion of large granular lymphocytes is an important effect of dasatinib therapy, shown to be an off-target phenomenon associated with pleural effusion and better clinical response. The benefit of dasatinib-induced lymphocytosis and its underlying mechanism of this are important points for clinicians working in hematology and oncology.

Keywords: Dasatinib; Large granular lymphocytosis; Immune regulation; Chronic myeloid leukemia; Pleural effusion; Response

1. Introduction

Dasatinib is a second generation tyrosine kinase inhibitor (TKI) with different efficacy and toxicity profiles from imatinib mesyate. Dasatinib inhibits TEC kinases and SRC family kinases which are the key regulators in immune

* Tel.: +90 322 3386060 3142; fax: +90 322 3386572.
E-mail address: sepay@cu.edu.tr

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responses [1–4]. Dasatinib is more potent than imatinib in the treatment of Ph^+ leukemias and with wider spectrum/efficacy, so the use of dasatinib will increase in coming years.

Increases in cytotoxic T and natural-killer cells in peripheral blood have been reported in cases treated with dasatinib in recent years. The awareness of the clonal expansion of large granular lymphocytes and beneficial effect of this clonal cells increased the interest to dasatinib in cases receiving this drug. The immune modulation that results from expansion of these cells may be an advantage of dasatinib, in addition to its direct kinase inhibition but this point is not clear [5]. It is well known that NK cells and cytotoxic CD8+ T cells are the main mediators of immune responses for anti-CML effect and this regulation relates to the interaction between killer cell immunoglobulin-like receptors (KIRs) and their HLA ligands [6]. Additionally, CML is one of the malignant disorders most susceptible to immune manipulation. Stem cell transplantation is the classic example of this as curative anti-leukemic effects are regulated by alloreactive cytotoxic lymphocytes [7].

In vitro studies suggest that dasatinib inhibits the activation and proliferation of T cells, but its action on the human immune system is not clear [8–10]. Due to SRC inhibition, there is transient drug off target effects with dasatinib using. Clonal expansion of large granular lymphocytes in cases receiving dasatinib therapy has been shown to be associated with pleural effusion and better outcome [11]. The mechanism underlying the observed effect in blood cells due to dasatinib is not clear. The SRC family kinases play an important role in leukocyte trafficking between intravascular regions and tissues, which is important in regulation of cell adhesion and movement [12]. Therefore, the inhibition of SRC kinase activity by dasatinib may influence the homing capacity of leukocytes, and the alteration in white blood cell counts [13].

Pleural effusion and/or pulmonary infiltrates are relatively frequent complications of dasatinib [14–17]. Their correlation with the development of clonal large granular lymphocytes is very important [1,15,18]. A side effect of a drug has been found to be useful for clinical outcome as in other targeted agents. In this review, dasatinib-related large granular lymphocytosis and pleural effusion are evaluated and discussed with clinical responses. Defining and understanding the mechanism of this phenomenon are vital for clinicians working in hematology and oncology.

2. Dasatinib and clonal large granular lymphocytes

2.1. Definition

Large granular lymphocytes are those having three or more large granules in one cell and these cells normally account for only 10–15% of circulating mononuclear cells [18]. Large granular lymphocytosis is defined as (1) an absolute lymphocyte count >3.000–3.600 $\times 10^9$/l and absolute large granular lymphocyte count >1.500 $\times 10^9$/l and (2) predominance of large granular lymphocytes in peripheral blood smears on at least one occasion during dasatinib treatment. Many recent reports have pointed out that the interval between dasatinib intake and blood sampling is 1–2 h. Stains with CD2, CD3, CD4, CD5, CD7, CD8, CD16, CD56 and CD57 have been used to detect these cells. The immunophenotypic character of these cells is variable. In some studies, predominance of T cell phenotype has been reported while in others, NK cell lineage has been reported as the predominant cell type [11,16,18–20].

2.2. Prevalence of large granular lymphocytosis associated with dasatinib

We do not know the exact prevalence of lymphocytosis in the course of dasatinib treatment. There is only one prospective study that shows lymphocytosis in CML cases treated with dasatinib or imatinib [21]. In this study, the prevalence evaluated in 34 patients at diagnosis and when on TKI treatment. Surprisingly, clonal cells were found in the majority of cases before treatment and this clone persisted at low levels in imatinib-treated cases. In contrast, large granular lymphocytes showed marked expansion in dasatinib treated cases and 90% of these cases had TCR rearrangements [21]. In a phase III dose optimization trial of dasatinib in cases with chronic phase CML, lymphocytosis was found in 28% [15]. Knowledge of dasatinib-related large granular lymphocytosis comes from retrospective studies of CML and Ph + ALL. Its prevalence during dasatinib series varies between 27% and 64%. Lymphocyte counts in these cases have been found to be as high as 20 $\times 10^9$/l [11,16,18–20,22–24]. Lymphocytosis, and specifically large granular lymphocytosis has not been reported in cases treated with nilotinib or imatinib [16,18]. The most comprehensive and informative data about lymphocytosis in dasatinib-treated cases was published by Mustjoki et al. [16]. They studied two cohorts. In the first, 22 cases (5 Ph + ALL, 3 CML-BC, 2 CML-AP, 12 CML-CP) treated with imatinib were evaluated for lymphocytosis and compared with 8 cases with CML without it. In this cohort, fifteen cases had cytotoxic T cells and 7 cases had the NK cell phenotype and 50% of these lymphocytes had LGL morphology. Mustjoki et al. also explored dasatinib-related lymphocytosis in 46 cases of Ph + ALL resistant or intolerant to imatinib. They found lymphocytosis in 6 cases (13%). Table 1 shows the dasatinib-induced lymphocyte/LGL increases, the median time to the detection, association between pleural effusion, and response to treatment.

In the majority of cases treated by dasatinib, CD16 and CD56 have been found to be positive while CD3 was positive or negative, TCR genes were detected in 60–80% of LGL (+) cases [18].