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Original Article

Reshape memory T cell landscape in CML patients' blood by tyrosine kinase inhibitors

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Abstract

Background: CML, a blood cancer characterized by excessive myeloid cell proliferation, stems from the BCR-ABL1 gene fusion. This research aimed to uncover why leukemic stem cells resist treatment and explore innovative immune-based therapies to improve patient outcomes.

Methods: This study investigated the immunologic phenotypes (CD8, CD27, CD197, and CD45RA) of T cell subsets (TN, TCM, TEM, and TEF) in the peripheral blood of chronic myeloid leukemia patients in the chronic phase who achieved a complete molecular response to tyrosine kinase inhibitors. The treatment-free remission (TFR) patients were compared to age- and gender-matched healthy volunteers using multicolor flow cytometry for analysis.

Results: Flow cytometry analysis unveiled notable shifts in CD8+ T cell subsets. CML-CP patients showed a marked decrease in central memory T cells (TCM), dropping to 7.2% of the CD8+ population. Conversely, these patients exhibited substantial increases in effector memory T (TEM) and effector T (TEF) cells, rising to 37.6% and 24.4% respectively. The most statistically significant change occurred in the CD8+ TEF subset. CML-CP patients displayed a 24.4% presence of these cells, compared to only 15.7% in control groups. These findings suggest a distinct immunological profile in CML-CP, potentially impacting disease progression and treatment strategies.

Conclusion: Tyrosine kinase inhibitors restore the distribution of memory T cells in patients with chronic myeloid leukemia (CML), but T cell exhaustion remains an issue. This situation highlights the need for alternative activation strategies to enhance immunity.

Keywords: T cell subsets, CML, Peripheral blood microenvironment, Flow cytometry, Tyrosine kinase inhibitor.

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Myeloid Leukemia (CML has seen a remarkable transformation in its prognosis over the past two decades, largely due to the introduction of tyrosine kinase inhibitors (TKIs). These targeted therapies have revolutionized CML treatment, offering patients a near-normal life expectancy and the ability to resume their daily activities (1, 2). TKIs work by inhibiting the tyrosine kinase produced by the BCR-ABL1 gene in leukemia cells, effectively halting or slowing the production of abnormal white blood cells (2-4). While TKIs have proven highly effective in managing CML, they are not without their challenges. Patients often face the prospect of lifelong therapy, which can lead to various side effects and impact their quality of life. Moreover, the financial burden of long-term TKI therapy on both patients and healthcare systems is significant (1, 5, 6). Emerging research indicates that a select group of individuals with chronic myeloid leukemia who attain and maintain a profound molecular remission might be candidates for ceasing their tyrosine kinase inhibitor therapy (1).

This breakthrough has ignited curiosity about the immune system's alterations throughout and following tyrosine kinase inhibitor therapy, with a particular focus on T lymphocyte responses. T lymphocytes are essential for the body's defense against malignancies, and preserving their balance is critical for sustaining this protective mechanism (7). Memory T cells, a key component of adaptive immunity, are of particular interest in this context. These cells are typically divided into subsets based on their functional properties and migration patterns. Central memory T cells (TCM) and stem cell memory T cells (TSCM) are especially important for long-term immune protection. However, the distribution and behavior of these memory T cell subsets in CML patients, especially in response to TKI treatment, remain poorly understood (7).

The peripheral blood serves as a window into the immune system, offering insights into the changes occurring in response to disease and treatment. In CML patients undergoing TKI therapy, alterations in the balance of memory T cell subsets in peripheral blood could provide valuable information about the immune system's response to treatment and potentially predict outcomes (8). Understanding these changes is not only academically interesting but also clinically relevant. As more CML patients achieve deep molecular responses and become candidates for TKI discontinuation, there is a growing need for biomarkers that can predict successful treatment-free remission. Changes in memory T cell subsets could potentially serve as such biomarkers (9).

Furthermore, characterizing the rebalancing of memory T cell subsets after TKI treatment could shed light on the long-term effects of these therapies on the immune system. This knowledge could inform strategies to enhance immune function in CML patients, potentially improving outcomes and quality of life (8, 9). To reshape the memory T cell landscape in CML patients' blood using TKIs, we propose a novel experimental approach combining single-cell RNA sequencing with T cell receptor (TCR) profiling and functional assays. This method would allow for a comprehensive analysis of T cell subsets and their functional states before, during, and after TKI treatment (10). The experiment would involve collecting peripheral blood samples from CML patients at diagnosis, during TKI therapy, and after achieving complete molecular remission. Using flow cytometry-activated cell sorting, we would isolate CD4+ and CD8+ T cells, then perform single-cell RNA and TCR sequencing. This approach would provide detailed information on T cell subset distributions, activation states, and clonal expansions (10, 11). Additionally, we would assess the functional capacity of these T cells through ex vivo stimulation assays, measuring cytokine production and cytotoxicity against CML cells. By correlating these results with clinical outcomes, we could identify specific T cell signatures associated with successful TKI treatment and long-term remission (11, 12).

The aim of this article was to explore the re-balancing of memory T cell subsets in the peripheral blood of CML patients following TKI treatment. By examining these changes, we hope to provide insights into the immunological consequences of TKI therapy, identify potential biomarkers for treatment response and eligibility for TKI discontinuation, and contribute to our understanding of long-term immune function in CML patients. This research may pave the way for more personalized treatment approaches and improved management strategies for CML patients undergoing TKI therapy.

Methods

Patients and samples: Peripheral blood (PB) specimens were obtained from a diverse group of subjects, including 20 individuals diagnosed with CML-CP, 24 patients undergoing treatment with TKIs, and 20 participants in TFR. Additionally, PB samples were collected from 30 healthy volunteers to serve as a control group. All patients in the TKI-treated cohort achieved a complete hematological response (CHR), as evidenced by BCR/ABL transcript levels dropping below the 10% threshold following TKI therapy.

This milestone is significant in assessing treatment efficacy and disease management. Interestingly, prior research has revealed that the immunological profile of T lymphocytes in CML patient’s exhibits variability based on the degree of molecular remission attained. This observation underscores the complex interplay between disease status, treatment response, and immune system dynamics in CML patients. The heterogeneity in T cell characteristics across different levels of molecular remission highlights the importance of considering the immunological landscape when evaluating treatment outcomes and planning therapeutic strategies for CML patients. This finding suggests that the immune system's response to treatment may be as crucial as the direct effects of TKIs on leukemic cells (18).

General features of the study groups: The mean age and standard deviation for patients with CML-CP were 47.8±9.9 years, with an age range of 18 to 64 years. For patients receiving TKIs, the mean age was 50.5±10.3 years, with an age range of 30 to 67 years. In the TFR group, the mean age

was 47±8.5 years, with an age range of 32 to 57 years. The gender distribution for CML-CP was 40% males and 60% females, while in the TKIs group it was 50% male sand 50% females, and in the TFR group it was 46.7% males and 53.3% females (table 1).

Flow cytometry analysis: The experimental protocol was executed as per the manufacturer's guidelines, with reagents prepared as follows: A working solution of erythrocyte lysis buffer was created by combining 1 part 10x concentrate with 9 parts purified H2O, yielding a 1x dilution. This mixture was then equilibrated to ambient temperature before application.

Aliquots of 100 µl anticoagulated whole blood were individually treated with 5 µl of the following fluorochrome-labeled antibodies: anti-CD8 (SK1 clone, Biolegend), anti-CD45RA (HI100 clone, Biolegend), anti-CCR7 (G043H7 clone, APC197, Biolegend), and anti-CD27 (O323 clone, PerCP-Cyanine 5.5, Biolegend). Parallel samples of 100 µl whole blood were set aside as unstained controls. All specimens were incubated in darkness for a quarter-hour at room temperature. Subsequently, 2 ml of the prepared 1x erythrocyte lysis buffer was introduced to both stained and control samples, followed by a further 10-minute dark incubation at ambient temperature. The samples underwent centrifugation at 2300 rpm for 5 minutes, after which the liquid phase was removed. The resulting cell pellets were rinsed with 2 ml of wash solution and re-centrifuged under identical conditions, again discarding the supernatant. The cell pellet was subsequently reconstituted in 0.5 ml of 1x stabilizing solution. Both experimental and reference samples were examined using a FACS Canto II flow cytometry device (BD Biosciences). Results were interpreted with DIVA software (2016 version). Each sample analysis encompassed at least 100,000 cellular occurrences, which were documented and evaluated.

Gating: Gating and hemato- pathologist advisor have been performed (13).

✓ A density plot of side scatter height (SSC-A) versus forward scatter area (FSC-A) was employed to isolate viable cells and eliminate debris.

✓ Forward scatter height (FSC-H) versus area (FSC-A) was used to select individual cells.

✓ An immunological gate of SSC versus CD8+ was applied to identify the CD8+ T lymphocyte population.

✓ Side scatter height (SSC-H) versus CD45RA was used to separately gate CD45RA+ and CD45RA- T cell subsets.

✓ Naïve CD8+ T cells were identified by CD45RA+ CCR7+ CD27+ markers.

✓ Central memory CD8+ T cells were characterized by CD45RA- CCR7+ CD27+ expression.

✓ Effector CD8+ T cells were defined by CD45RA- CCR7- CD27+ markers.

✓ Effector memory CD8+ T cells were identified by CD45RA+ CCR7- CD27- expression. These gating strategies are illustrated in figures 1, 2, 3, and 4.

Table 1. Some properties of the studied groups

Characteristics	Control No. 30	CML-CP No. 20	TKIs No. 24	TFR No. 15
Age mean (range) years	49.0 (20-66)	47.8 (18-64)	50.5 (30-67)	47 (32-57)
Male No. (%)	15 (50)	8 (40)	12 (50)	7 (46)
Female No. (%)	15 (50)	12 (60)	12 (50)	8 (54)
Treatment duration, mean (range), days	NA	NA	150 (30-276)	NA

CML-CP: Chronic Myeloid Leukemia-Chronic Phase, TKIs: Tyrosine Kinase Inhibitors and TFR: Treatment Free Remission.

Statistical analysis: The statistical evaluation was executed using GraphPad Prism 10.0.0, a comprehensive data analysis tool designed for Windows platforms, developed by GraphPad Software in San Diego, California. For inferential statistics, one-way ANOVA was employed, with statistical significance established at $p < 0.052$.

The study's findings were visually represented through a variety of methods, including tabular summaries, bar graphs, scatter diagrams, and trend curves, which effectively illustrated key descriptive measures such as the data spread, arithmetic average, central value, and measure of dispersion. This multifaceted approach to data visualization and statistical analysis provided a thorough examination of the dataset, enabling clear interpretation and communication of the research outcomes.

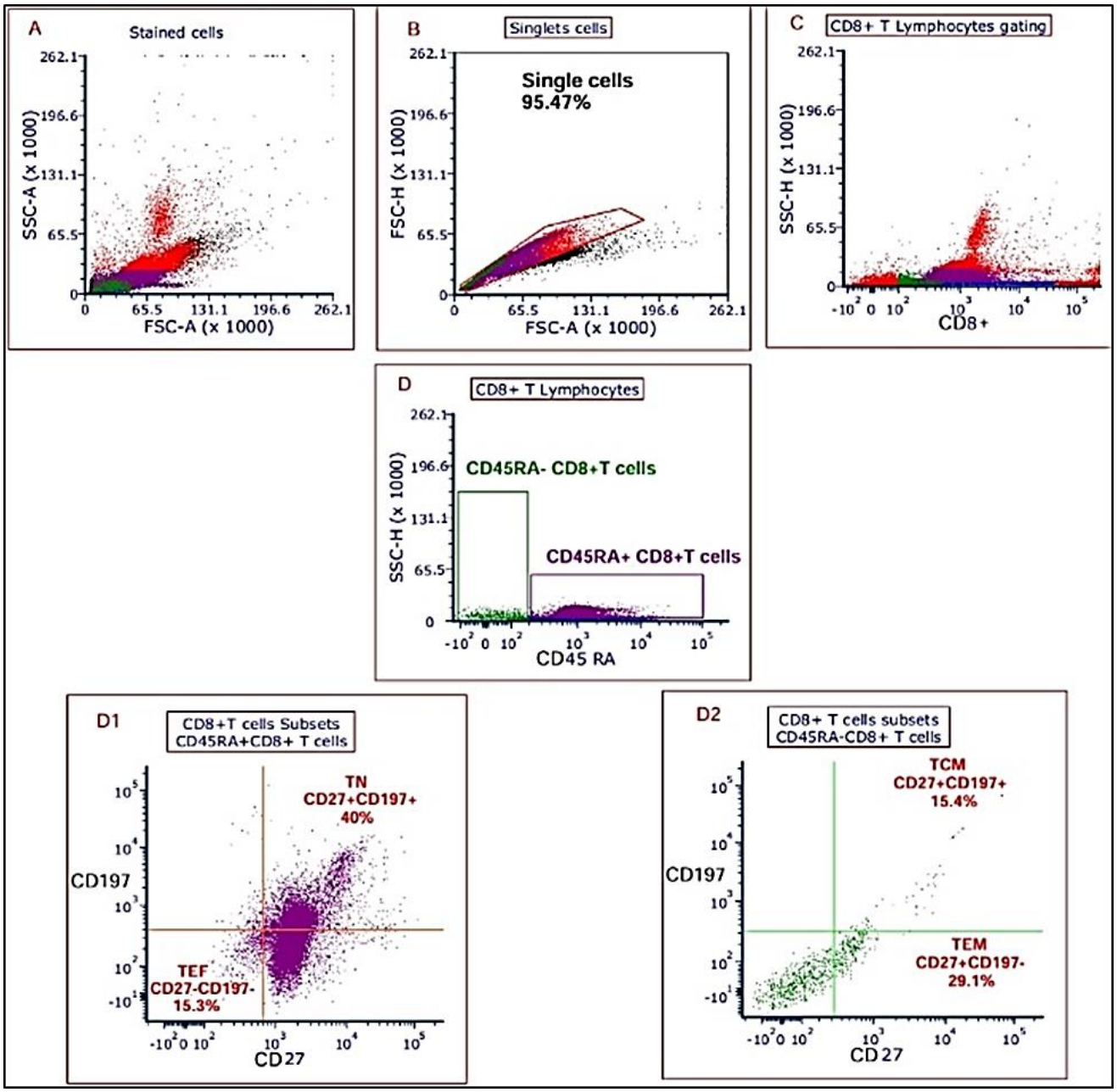

Figure 1. Cytometric examination of the control cohort specimen is illustrated as follows: A) Scatter plot depicting fluorescently labeled cellular entities. B) Scatter plot employed for isolating individual cellular units. C) Scatter plot highlighting CD8-positive lymphocytes. D1) Scatter plot delineating CD45RA+CD27+CD197+ subpopulation (denoted as TN) and CD45RA+CD27-CD197- subpopulation (denoted as TEF). D2) Scatter plot distinguishing CD45RA-CD27+CD197+ subpopulation (denoted as TCM) and CD45RA-CD27+CD197- subpopulation (denoted as TEM). Key to T lymphocyte subsets; TN: Antigen-inexperienced T lymphocytes, TCM: T lymphocytes with central recall capacity, TEM: T lymphocytes with peripheral recall capacity, TEF: Terminally differentiated T lymphocytes

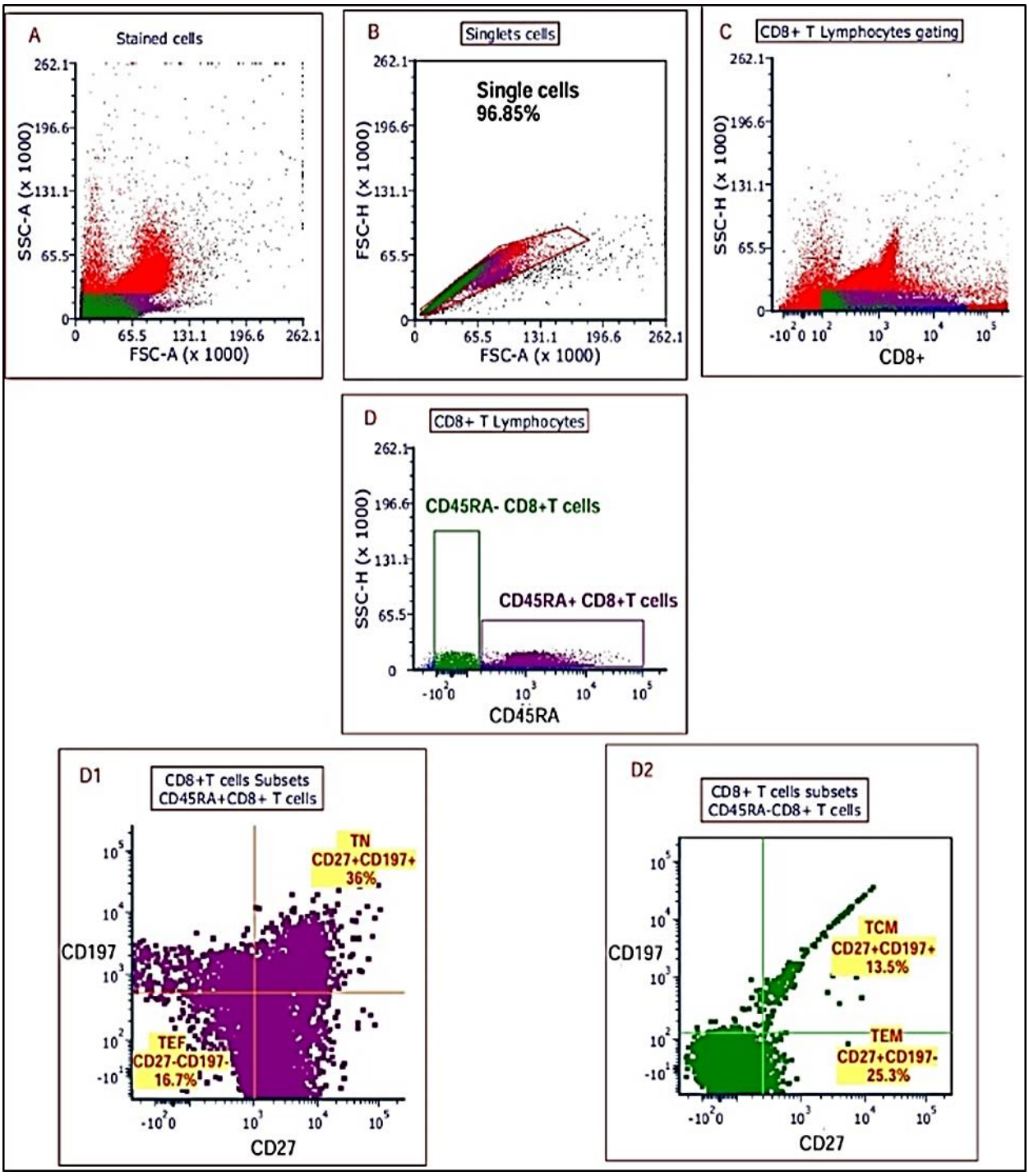

Figure 2. Cytometric evaluation of the CML-CP group specimen is presented as follows: A) Bivariate distribution plot showcasing fluorochrome-tagged cellular elements. B) Bivariate distribution plot utilized for discriminating solitary cellular entities. C) Bivariate distribution plot emphasizing CD8-expressing T lymphocytes. D1) Bivariate distribution plot demarcating the CD45RA+CD27+CD197+ subgroup (labeled as TN) and the CD45RA+CD27-CD197- subgroup (labeled as TEF). D2) Bivariate distribution plot differentiating the CD45RA-CD27+CD197+ subgroup (labeled as TCM) and the CD45RA-CD27+CD197- subgroup (labeled as TEM). Glossary of T lymphocyte subpopulations; TN: Antigen-naive T cells, TCM: T cells with central memory function, TEM: T cells with effector memory capabilities, TEF: Terminally differentiated effector T cells

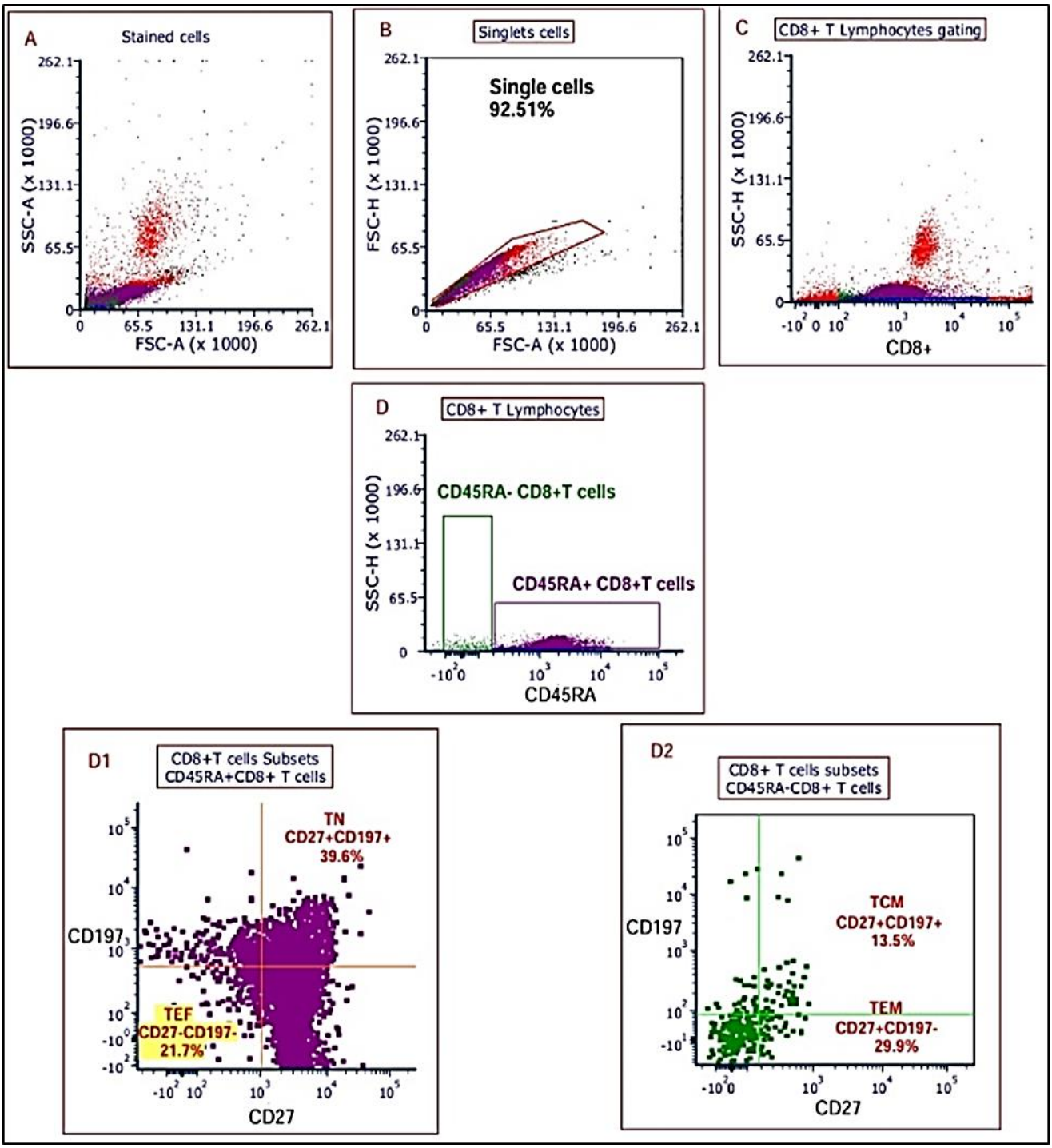

Figure 3. Cytometric assessment of the TKI-treated cohort sample is illustrated as follows: A) Scatter diagram depicting fluorescently-labeled cellular components. B) Scatter diagram employed to isolate individual cell units. C) Scatter diagram highlighting CD8-positive T lymphocytes. D1) Scatter diagram delineating the CD45RA+CD27+CD197+ subset (designated TN) and the CD45RA+CD27-CD197- subset (designated TEF). D2) Scatter diagram distinguishing the CD45RA-CD27+CD197+ subset (designated TCM) and the CD45RA-CD27+CD197- subset (designated TEM). T lymphocyte subpopulation nomenclature; TN: Antigen-inexperienced T cells, TCM: T cells with central recall functionality, TEM: T cells with peripheral recall functionality, TEF: Terminally differentiated T cells with effector properties

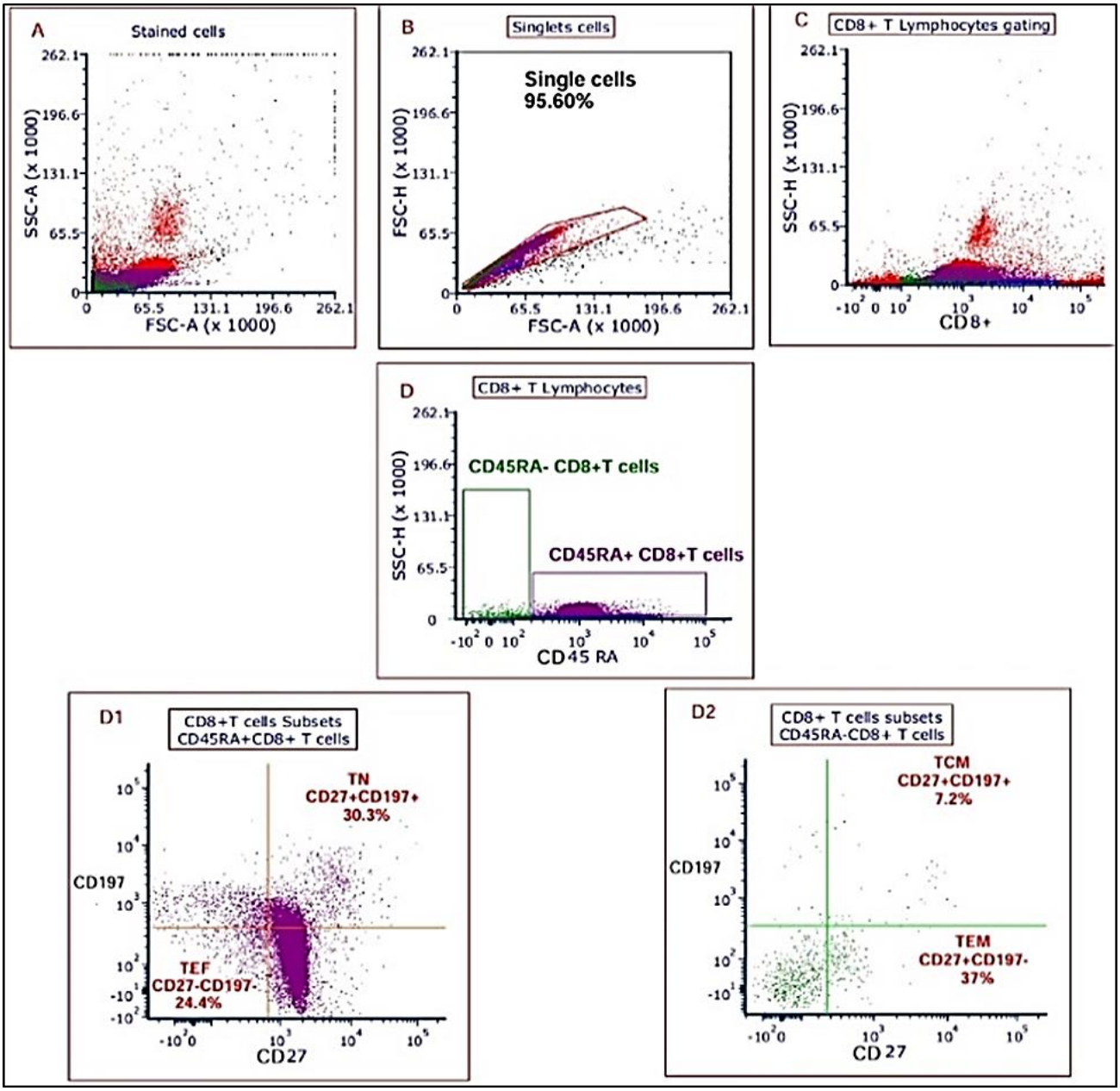

Figure 4. The flow cytometric examination of the TFR cohort specimens involved a series of scatter plots for comprehensive immunophenotyping. Initially, fluorescently labeled cellular populations were visualized, followed by the isolation of individual cell events. Subsequent analysis focused on CD8-positive T lymphocytes, with further delineation of specific subsets based on their surface marker profiles. Two key scatter plots were utilized to distinguish between four distinct T cell populations: naive T cells (TN, CD45RA+CD27+CD197+), terminal effector T cells (TEFF, CD45RA+CD27-CD197-), central memory T cells (TCM, CD45RA-CD27+CD197+), and effector memory T cells (TEM, CD45RA-CD27+CD197-). This multifaceted approach allowed for a nuanced characterization of the T cell landscape within the TFR group sample, providing valuable insights into the distribution of these functionally diverse lymphocyte subpopulations.

Results

The study's methodology for identifying CD8+ T cell subsets is detailed in the appendices, specifically table 2. T lymphocytes are pivotal in the immune response, with TN cells initiating the process by recognizing antigens presented by APCs and interacting with costimulatory molecules on dendritic cells. This interaction triggers their differentiation into various effector and memory subsets. Post-pathogen clearance, a select few effector cells evolve into long-lasting TCM, providing rapid response

capabilities upon reinfection. To delve deeper into the immunophenotypic variations among T cell subsets, CD8+ T cells were categorized based on their expression of CD45RA, CD27, and CCR7 markers. These categories included TN, TCM, TEF, and TEM cells. The research team examined the activated, inhibitory, and senescent characteristics of each subset across patient groups and controls. Interestingly, when analyzing the distribution of these subsets within CD8+ T cell populations, no significant disparities were observed in the proportion of CD8+ TN cells among the control group and various patient cohorts, including those with CML-CP, those undergoing TKIs, and those in TFR, as illustrated in figure 5. This investigation revealed a notable alteration in the distribution of central memory CD8+ TCM across different patient cohorts. Specifically, individuals in the CML-CP exhibited a marked reduction in CD8+ TCM cells, with levels dropping to 7.2% compared to the 14.7% observed in healthy controls, a difference that reached statistical significance (P = 0.001). Interestingly, this diminution was not replicated in patients undergoing tyrosine kinase inhibitor therapy (TKIs) or those who had achieved treatment-free remission (TFR). The TKIs group maintained a CD8+ TCM percentage of 13.52% (P = 0.88 versus controls), while the TFR cohort showed levels of 14.5% (P = 0.988 versus controls), both statistically indistinguishable from the control group.

These findings, illustrated in figure 6, suggest that the depletion of CD8+ TCM cells may be a characteristic of active, untreated CML, potentially reversible with successful therapy. The study examined the distribution of TEM and TEF CD8+ T cell subsets, which are highly specialized in producing cytotoxic molecules for immune defense against pathogens and malignancies. In patients with CML-CP, there was a notable increase in both CD8+ TEM (37.6%) and TEF (24.4%) populations. However, statistical significance was only reached for the CD8+ TEF subset, which showed a marked elevation compared to healthy controls (24.4% vs. 15.7%, P = 0.037). Interestingly, no significant alterations were observed in these subsets among patients undergoing TKIs or those in TFR. Nevertheless, a subset of TKI-treated patients displayed elevated levels of CD8+ TEM and TEF cells, potentially indicative of their remission status. These findings, depicted in figures 7 and 8, suggest that the expansion of cytotoxic T cell subsets may be a characteristic feature of active CML, with potential implications for disease monitoring and treatment response assessment.

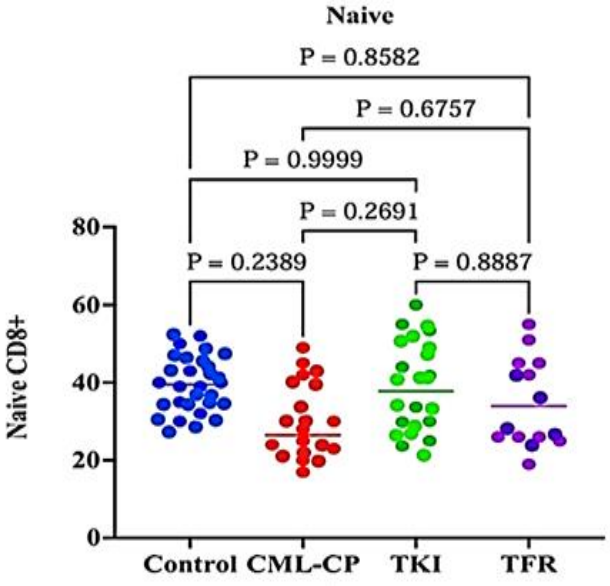

Figure 5. The prevalence of naive CD8+ TN across various subject groups. The cohorts included patients with CML-CP, individuals undergoing TKIs, and those who had achieved TFR. The analysis focused on comparing the distribution of this specific T cell subset among these distinct clinical categories, providing insights into the immunological landscape associated with different stages of CML management.

Table 2. Comparison of percentage of CD8+ T cell subsets in study groups.

CD8+ T cells Subsets (%)	Mean+SD				P-value
	Control No. 30	CML-CP No. 20	TKIs No. 24	TFR No. 15	
CD45RA+ CCR7+ CD27+	40±7.0	30.3±11.12	39.64±13.15	36±12.8	0.2102
CD45RA- CCR7+ CD27+	15.45±6.6	7.2±3.7	13.54±6.7	14.5±5.5	0.0128*
CD45RA- CCR7- CD27+	15.7±10.07	24.4±13.5	21.72±12.3	16.7±9.2	0.2877
CD45RA+ CCR7- CD27-	29±11.3	37.6±15.3	29.94±11.9	25.3±13.2	0.2155

Significant P value <0.05 / Highly Significant P- value <0.01

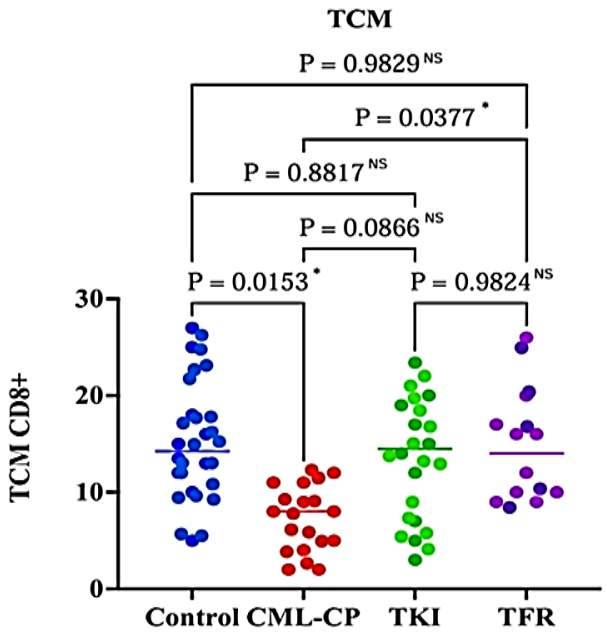

Figure 6. Frequency of Central Memory T CD8+ TCM in groups study

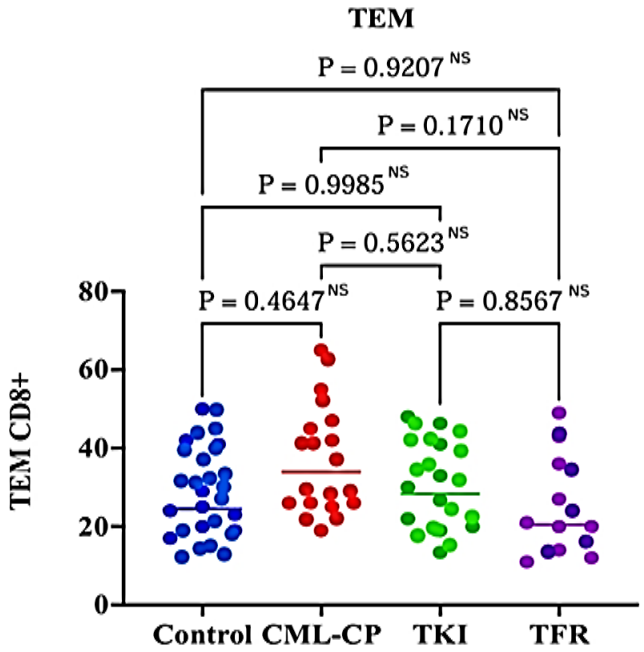

Figure 7. Frequency of Effector Memory T CD8+ TEM in groups study

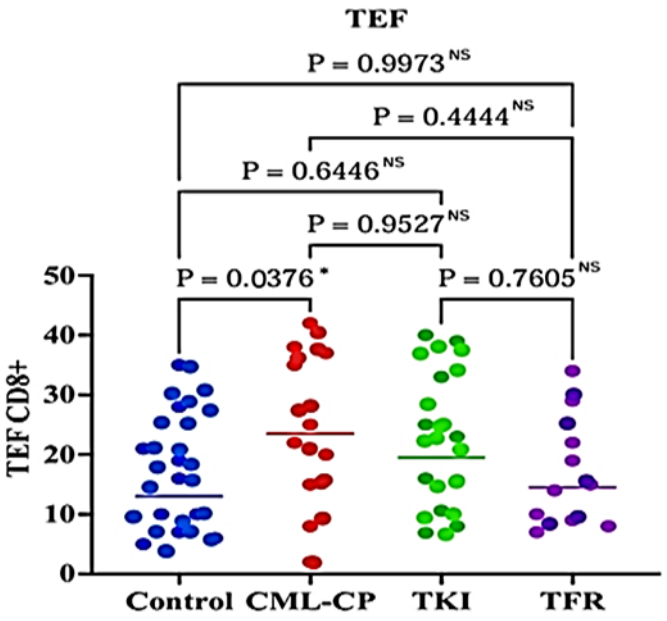

Figure 8. Frequency of Effector T CD8+ TEF in groups study

Discussion

It has been focused on three distinct subsets of cytotoxic lymphocytes: natural killer (NK) cells, CD8-positive T lymphocytes, and gamma-delta (γδ) T cells. These specialized immune cells play a crucial role in the body's defense against hematological malignancies, including their ability to target and eliminate CML cells. The study highlights the intricate interplay between the innate and adaptive arms of the immune system in cancer surveillance and eradication. Specifically, it underscores the importance of NK cells, CD8+ and CD4+ T lymphocytes, along with their associated effector molecules and endogenous signaling cascades, in mounting a comprehensive anti-tumor response. This research emphasizes the critical function of these immune components in safeguarding the host against neoplastic threats, particularly in the context of CML and related hematological disorders (14). Research has identified leukemia-associated antigen (LAA)-specific

cytotoxic T lymphocytes (CTLs) in the blood of patients with chronic phase chronic myeloid leukemia (CP CML). These immune cells recognize and target the BCR-ABL fusion protein, as well as other selectively expressed or overexpressed LAAs, including proteinase-3 (PR3) and Wilms' tumor antigen 1 (WT1), potentially contributing to the immune system's regulation of CML. However, studies have revealed that T cells from untreated CML patients exhibit compromised functionality, characterized by diminished expression of the TCRζ chain, impaired cytotoxic capabilities, and a lack of immunoregulatory cytokine production. These findings suggest a complex interplay between the immune system and CML pathogenesis, highlighting both the presence of tumor-specific immune responses and the functional deficits that may limit their effectiveness in controlling the disease (15). In this investigation, we found that the immunophenotype of CD8+ T cell subsets (TN, TCM, TEM, and TEF) was associated with disease status and location.

This comprehensive analysis of T cell subsets in chronic myeloid leukemia (CML) patients reveals nuanced changes in activation and proliferation markers, despite minimal alterations in the overall CD8+ population (16). Contrary to some studies suggesting insufficient activation of early differentiated T cells (TN and TCM) in CML patients, particularly those on TKI therapy, other research indicates that TEM and TEF subsets may be largely normal in complete responders, with some patients showing elevated levels potentially correlated with remission extent. The observed shift towards more differentiated T cell subsets is not unique to CML, as similar patterns have been noted in head and neck squamous cell carcinoma patients, with advanced-stage disease associated with higher levels of activated TEM and TEF cells. While these findings suggest that T cells in CML patients may differentiate more rapidly into effector cells, questions remain about their full immune functionality (17).

TKI treatment appears to play a role in restoring T cell subset balance. However, some studies indicate that early differentiated subsets may still show insufficient activation, while effector subsets display various exhausted phenotypes across different CML stages. This complex picture suggests potential impairment of long-term immunological surveillance and reduced capacity for leukemia cell elimination, highlighting the intricate interplay between CML progression, treatment, and T cell functionality (16). Our flow cytometry analysis of peripheral blood lymphocytes revealed a markedly increased ratio of TCM to TN CD8+ T cells in the study participants. This observation aligns with previous research showing elevated levels of CD3+CD8+CD45RO+ memory T cells in similar patient populations. Notably, the expanded CD8+ T cell population predominantly expressed CD45RO+, a phenomenon also documented in patients undergoing TKI therapy (18). Interestingly, a separate study demonstrated (19) the persistence of memory and effector CTLs and NK cells in a patient who had been in treatment-free remission for 2.4 years, despite normal lymphocyte counts. These findings collectively suggest that dasatinib treatment may enhance cellular immunity, particularly involving NK cells and CTLs, with effects potentially lasting long after treatment discontinuation. This research provides valuable insights into the long-term immunological impact of TKI therapy in chronic myeloid leukemia patients, highlighting the potential for sustained immune modulation even after achieving treatment-free remission.

The advent of TKIs like imatinib, bosutinib, and nilotinib has dramatically improved survival rates for CP-CML patients, with life expectancies now comparable to those with chronic conditions such as hypertension and diabetes (20). However, TKIs cannot completely eliminate CML stem cells, necessitating ongoing treatment. While studies show that approximately half of patients can safely discontinue TKI therapy under specific conditions, the criteria for safe discontinuation remain unclear (21). Interestingly, patients achieving treatment-free remission after interferon alpha therapy demonstrated enhanced cellular immunity, including increased CD8+ T cells and NK cells. Additionally, allogeneic donor lymphocyte infusion has shown efficacy in treating relapsed CML patients (22). These findings highlight the critical role of bolstering cellular immunity in eradicating CML stem cells and achieving treatment-free remission. TKIs not only inhibit BCR-ABL but also target other tyrosine kinases, resulting in TEM and TEF T cells emerging as key subsets for efficient pathogen clearance. This research could potentially lead to the development of more targeted anti-leukemia immunotherapies by further exploring the underlying mechanisms of TEM and TEF subset dysfunction in CML patients (23).

This research illuminates the pivotal role of CD8+ T cell subsets in CML progression and treatment response. The findings suggest that persistent exposure to leukemic cells and their microenvironment may lead to T cell exhaustion. Notably, the study demonstrates that successful leukemia cell elimination through TKI therapy can normalize memory T cell distributions. However, the research emphasizes the need for additional T cell activation strategies to bolster overall immune function in CML patients, including those responding optimally to TKIs. The

observed reduction in TN and TCM CD8+ T cells, particularly in chronic phase CML (CML-CP) patients, indicates suboptimal T cell activation. Furthermore, the accumulation of potentially exhausted TEM and TEF cells in CML patients suggests T cell dysfunction. The varying degrees of this accumulation and exhaustion may significantly influence patients' responses to TKI therapy and their overall prognosis. These insights underscore the complex interplay between the immune system and CML pathogenesis, highlighting potential avenues for immunotherapeutic interventions to complement existing treatments.

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Ethics approval: The study design was accepted by research Ethical Committee and Scientific Committee designated by Biology Department, College of Science, University of Baghdad under the reference number (NO.: CSEC/0922/0111 September 29, 2022).

Conflict of interests: The authors declare no conflict of interest in the conduct of the study.

Authors' contribution: All authors of this work were equally involved in the research and writing process of the publication.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

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