Clinical Impact of CD200 on Outcome of Acute Myeloid Leukemia: A Cohort Study from a Single Center

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Abstract

Purpose CD200, a trans-membrane protein belonging to the immunoglobulin superfamily, has been associated with a poor prognosis in acute myeloid leukemia(AML). We aimed to analyze the correlations between CD200 expression and prognostic significance in AML patients.

Methods We retrospectively reviewed 160 AML patients evaluating the impact of CD200 expression on complete remission (CR), disease free survival(DFS), and overall survival (OS) in our institution between 2018 and 2021.

Results CD200 were expressed in 100/160 (62.5%) cases, which were defined as the CD200 positive (CD200+) group and the rest of 60 cases were identified as CD200 negative(CD200-) group. A higher incidence of CD34 expression (P < 0.0001), NPM1 mutated(P=0.001) and unfavorable cytogenetic/molecular (P <0.0001) cases in CD200+ group. More intermediate cytogenetic/molecular status(P<0.0001) in CD200-group. Complete remission (CR) was evaluable achieved in70 patients (43.75%):34/100 (34%) in CD200+ and 36/60 (60%) in CD200- group (P = 0.001). CD200+ patients had significant lower probability to attain complete remission after first induction chemotherapy, both in univariate (P = 0.002) and multivariate (P = 0.023) analysis. In the whole population, CD200 expression had no significant effect on DFS (P = 0.837) and OS (P =0.155). In subgroup analysis we demonstrated that CD200 has obvious negative impact on OS in less-intensive approaches (P = 0.006) and in chemotherapy-only treatment (p=0.032) patients.

Conclusion Expression of CD200 in AML contributes to low-remission rate and with a further worsening in long-term survival in patients receiving less-intensive approaches and chemotherapy-only treatment. CD200 positive is an indicator for low remission and poor prognosis in subgroups.

1. Introduction

Despite higher rate of complete remission(CR) and long-term survival with induction chemotherapy and improvements in allogenic and autologous hematopoietic stem cell transplantation ,relapse and deaths occurs in the majority of acute myeloid leukemia (AML) patients(Pulte et al. 2008). The ultimate obstacle to curing AML is the elimination of leukemia stem cells (LSCs), self-renewal, relative quiescence, resistance to apoptosis, and therapy-resistant cells and deemed the source of relapse(Thomas and Majeti 2017). In allogeneic stem cell transplant, graft-versus-leukemia (GvL) response are capable of eliminating LSCs and curing AML patients, which is the evidence that LSCs can be destruction via immune response. However other treatments such as chemotherapy, targeted therapy or immunotherapies are insufficient to cure disease because they are not directed against LSCs(Daver et al. 2019; Herbrich et al. 2021).

CD200 is a transmembrane cell surface type I glycoprotein, also called MOX-2, which is a member of the immunoglobulin superfamily(Barclay et al. 2002).CD200 is normally expressed in diverse cell types and tissues, such as endothelium, thymocytes, and populations of lymphocytes, CD200 and the CD200-receptor (CD200R) expression is restricted to myeloid lineage cells , pointing the regulation of CD200 is

confined to myeloid-derived cells(Barclay et al. 2002; Hoek et al. 2000). Mechanistically, CD200 binds to CD200R is correlated with suppressed NK and memory CD4+ T cell function resulting in low immune response(Hoek et al. 2000; Wong et al. 2010). In AML, CD200 is selectively overexpressed in LSCs and can be used to identify LSCs activity (Herbrich et al. 2021; Ho et al. 2020). Clinically, CD200 expression on AML has been associated with reduction of complete remission and significantly worse overall survival (Damiani et al. 2015; Herbrich et al. 2021; Tiribelli et al. 2017). Taken together, this suggests that CD200 plays a disadvantageous role in AML remission and long-term survival. Since the relative paucity of data and the somehow conflicting results, we evaluated the impact of CD200 expression on response to therapy in AML patients and treatment-defined subgroups.

2. Patients And Methods

2.1 patients

One hundred sixty patients diagnosed as non-promyelocytic AML treated with at least one cycle chemotherapy at our Institutions between 2018 and 2021, were included in this analysis. Cytological diagnosis was performed based on bone marrow and peripheral blood. Multiparametric flow cytometry (DxFLEX-Beckman Coulter) was employed to evaluate leukemia-associated antigens. CD200 was expressed as the percentage of positive cells (with 50% as a cut-off value). Cytogenetic risk was classified according to Medical Research Council criteria(Grimwade et al. 2010). Cytogenetic/molecular risk defined as at least one of the unfavorable cytogenetic or combined genetic risk.

2.2. Treatment protocol

All patients received induction chemotherapy including the standard chemotherapy based on cytarabine + anthracycline (7 + 3) in and less-intensive approaches including hypomethylating agents (azacytidine or decitabine), low-dose cytarabine, venetoclax, liposomal doxorubicin. Then patient proceeded to allogeneic stem cell transplantation(allo-SCT), autologous stem cell transplantation(auto-SCT) or repeated chemotherapy consolidation(chemotherapy-only).

2.3. Statistical analysis

Complete remission (CR) was defined as complete peripheral hematological recovery and the absence of bone marrow disease upon morphological, immunophenotypic, or molecular evaluation. Over-all survival (OS) was calculated from diagnosis to death (irrespective of its cause). Disease-free survival (DFS) was defined as the time from the date of CR to the date of relapse of AML. Patients lost to follow-up were censored at the time last seen alive. Categorical variable was compared with Fisher exact test or Yates corrected chi square test, as required. Comparisons between continuous variables were evaluated by T student test or by Kruskall Wallis test. Factors affecting CR were assessed by univariate and multivariate logistic regression, and expressed as HR (95%CI). OS curves were constructed by Kaplan Meier method and differences among groups calculated by log-rank test. The Cox proportional hazard regression model was used to examine the potential prognostic factors for OS and DFS: all variables with p values ≤ 0.05

in univariate analysis were included in the multivariable model and a backward stepwise procedure was applied to identify significant factors. All p-values are 2-sided at a significance level of 0.05. Statistics was performed by IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 22 (SPSS Inc., Chicago, IL) and GraphPad Prism, version 8.01 (GraphPad Software).

3. Results

This study was performed in 160 AML patients, 89 (55.6%) were male, 71 (44.4%) were female, and the median age was 54 years (range, 12–88years). De novo AML was found in 112/160 (70%) patients. Forty patients (25%) had high white blood cell (WBC) counts at diagnosis, defined as $\geq 50x10^9$/L. The cytogenetic/molecular risk was favorable in 23/160 (14.4%) cases, intermediate in 65/160(40.6%), unfavorable in 56/160 (35.0%). CD34 was expressed in 119/160 (74.4%) patients, and FLT3-ITD and NPM1 mutations were detected in only 19/160 (12%) patients, respectively. As for treatment, 88(55.0%) cases received standard cytarabine + anthracycline (7 + 3) chemotherapy, 72(45.0%) had less-intensive approaches. One-hundred seven patients (66.9%) received chemotherapy-only treatment whereas 38(23.7%) cases proceeded to allo-SCT and 15 patients(9.4%) received auto-SCT.

CD200 was positive in 100/160 (62.5%) cases. So according to the CD200 expression, the whole population were defined as the CD200 positive (CD200+) group and CD200 negative(CD200-) group , respectively. The relevant information of the patients at diagnosis in two groups was shown in Table 1. There was no difference in age, sex, WBC count, de novo acute leukemia, secondary leukemia, induction and consolidation chemotherapy between the two groups. CD200+group had more cytogenic/molecular unfavorable cases than CD200- group (56.0% vs 26.7%, p <0.001).CD200 was more frequently expressed in CD34 positive blast cells (p < 0.0001), while there was an inverse correlation with intermediate cytogenetic risk in two groups (30.0% vs 57.3%, p <0.001). NPM1 mutation less frequently in CD200+ group than CD200- group (5.0% vs 23.3%, p =0.0001).

All patients received induction chemotherapy and were evaluable for response. Factors affecting CR probability are listed in Table2.In univariate analysis, secondary disease (p = 0.012), unfavorable cytogenetic/molecular risk (p < 0.001) or CD200 positive were associated with reduced probability to achieve CR. CR was obtained in 34/100 (34%) in CD200+ and in 36/60 (60%) CD200- cases (p = 0.001). Patients with aberrant CD200 expression had near threefold less probability to obtain CR (HR 0.343, 95% CI 0.117–0.666). In multivariate analysis statistical significance was maintained by CD200(HR 0.438, 95% CI 0.214-0.894, p = 0.023) along with unfavorable cytogenetic risk (HR 0.304, 95% CI 0.112-0.820, p = 0.019).

Table 1

Clinical/biological characteristics at diagnosis

	CD200+group(n=100)	CD200-group(n=60)	*p*
Age≥60yrs: n, (%)	46(46.0)	27(45.0)	0.902
Sex: M/F: n, (%)	36(36.0)	53(88.3)	0.388
WBC ≥ 50×10^9 /L: n, (%)	25(25.0)	15(25.0)	1
Type of leukemia:			0.557
De novo: n, (%)	76(76.0)	36(60.0)	
Secondary: n, (%)	24(24.0)	24(40.0)	
Cytogenetic/molecular risk:			
Favorable: n, (%)	15(15.0)	8(13.3)	0.771
Intermediate: n, (%)	30(30.0)	36(60.0)	<0.001
Unfavorable: n, (%)	56(56.0)	16(26.7)	<0.001
CD 34 positive: n, (%)	94(94.0)	25(41.7)	<0.001
Flt3-ITD:			0.050
mutated: n, (%)	8(8.0)	11(18.3)	
wild type: n, (%)	90(90.0)	46(76.7)	
NA: n, (%)	2(2.0)	3(5.0)	
NPM1:			0.001
mutated: n, (%)	5(5.0)	14(23.3)	
wild type: n, (%)	90(90.0)	42(70.0)	
NA: n, (%)	5(5.0)	4(6.7)	
Response to induction:			0.001
CR1: n, (%)	34(34.0)	36(60.0)	
No CR1: n, (%)	66(66.0)	24(40.0)	
Standard induction chemotherapy: n, (%)	58(58.0)	30(50.0)	0.325
consolidation therapy			
Auto-SCT: n, (%)	9(9.0)	6(10.0)	0.834
Allo-HSCT: n, (%)	26(26.0)	12(20.0)	0.388
Chemotherapy-only: n, (%)	65(65.0)	42(70.0)	0.367

Abbreviations yrs years old, WBC white blood cell count, CR1 complete remission after induction therapy, Auto-SCT autologous stem cell transplantation , Allo-SCT allogeneic stem cell transplantation , chemotherapy-only repeated chemotherapy consolidation.

Table 2

Uni and multivariate analysis of potential factors for CR

Univariate			Multivariate	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Age ≥60yrs	0.667（0.354-1.254）	0.209		
Secondary leukemia	0.344（0.150-0.791）	0.012	0.470(0.118-1.177)	0.107
WBC（≥50× 10^9/L）	0.615（0.293-1.293）	0.200		
NPM1 mutated	1.911（0.724-5.042）	0.191		
FLT3 mutated	1.180（0.452-3.083）	0.735		
Intermediate cytogenetic/molecular risk	2.771（1.444-5.315）	0.002	0.922(0.353-2.411)	0.869
Unfavorable cytogenetic/molecular risk	0.231(0.117-0.456)	<0.001	0.304(0.112-0.820)	0.019
CD200 positive	0.343（0.117-0.666）	0.002	0.438（0.214-0.894）	0.023
CD34+	0.667（0.327-1.360）	0.265		
Standard induction therapy	1.593(0.845-3.003)	0.150		

Abbreviations yrs years old, WBC white blood cell count,CR1 complete remission after induction therapy, Auto-SCT autologous stem cell transplantation , Allo-SCT allogeneic stem cell transplantation , chemotherapy-only repeated chemotherapy consolidation.

At the time of analysis, 51/160 patients had relapsed and 109/160 remained in CR. Factors affecting DFS in uni- and multivariate analysis are listed in Table 3. CD200 expression, per se, did not impact on DFS. In univariate analysis an adverse effect on DFS was found for age ≥60yrs (HR 1.938, 95%CI 1.320-2.844, *p* =0.001),secondary leukemia(HR 1.821, 95%CI 1.195-2.774, *p* =0.005), standard chemotherapy

(HR 1.821,95%CI 1.195-2.774,*p*=0.005) or unfavorable cytogenetic/molecular (HR 2.382, 95%CI 1.622-3.497, *p* <0.001),while there was an positive effect with NPM1 mutated (HR 0.480, 95%CI 0.249-0.929, *p* =0.029), CR1(HR 0.457 ,95%CI 0.309-0.677, *p* <0.001) ,and allo-SCT(HR 0.407 ,95%CI 0.244-0.677,P=0.001). Multivariate analysis confirmed their positive role for DFS by NPM1 mutated (HR 0.487,95% CI 0.236-0.956, *p=0.043*) , CR1 (HR 0.518,95% CI 0.330-0.774, *p=0.002*) and allo-SCT (HR 0.187,95%CI 0.041-0.927, *p=0.036*) . Unfavorable cytogenetic/molecular risk retained their negative prognostic role(HR 1.594, 95%CI 1.049-2.423).

Table 3

Uni and multivariate analysis of factors for DFS

	HR (95%CI)	p	HR (95%CI)	p
Age ≥60yrs	1.938(1.320-2.844)	0.001	1.007(0.639-1.817)	0.780
Secondary leukemia	1.821(1.195-2.774)	0.005	1.048(0.654-1.679)	0.845
WBC≥50×10^9/L	1.383（0.779-2.456）	0.269		
NPM1 mutated	0.480(0.249-0.929)	0.029	0.487(0.243-0.978)	0.043
FLT3 mutated	0.922(0.506-1.679)	0.791		
Unfavorable cytogenetic/molecular risk	2.382（1.622-3.497）	<0.001	1.594(1.049-2.423)	0.029
Standard chemotherapy	1.821（1.195-2.774）	0.005	1.229(0.733-2.062）	0.434
CD200 positivity	1.042（0.708-1.533）	0.837		
CR1	0.457(0.309-0.677)	<0.001	0.518(0.339-0.791)	0.002
Allo-SCT	0.407（0.244-0.677）	0.001	0.187(0.039-0.893)	0.036

Abbreviations yrs years old, WBC white blood cell count,CR1 complete remission after induction therapy, Auto-SCT autologous stem cell transplantation , Allo-SCT allogeneic stem cell transplantation , chemotherapy-only repeated chemotherapy consolidation.

We then evaluated the long-term survival, 80 (50%) cases had died, with a 1-year OS in the whole population was 48.2%(95%CI 43.6-52.8),2-year OS 35.1%(95%CI 30-40.2) (Fig. 1).As shown in Table 4 and Figure 1, in entire population, CD200 did not had impact on OS(*p*=0.155). In univariate analysis OS was

negatively affected by age of ≥60yrs (HR 2.346, 95%CI1.494-3.683, P<0.001), secondary AML (HR 12.034, 95%, CI 1.266-3.270, *p* =0.003), unfavorable cytogenetic/molecular risk(HR2.804 ,95%CI 1.772-4.432, *p* <0.001), standard chemotherapy(HR 2.034, 95% CI 1.266-3.270, *p* =0.003), chemotherapy-only (HR2.798, 95%CI 1.663-4.649, *p* =0.003),and Auto-SCT(HR3.295, 95%CI 1.202-9.029, *p* =0.020). In multivariate analysis, statistical significance was retained by age of ≥60yrs (HR 1.898, 95% CI 1.061-3.398, *p* =0.031), unfavorable cytogenetic/molecular status (HR 1.974, 95% CI 1.201-3.246, *p* =0.007), standard chemotherapy (HR 2.456, 95% CI 1.352-4.462, *p* =0.003), Auto-SCT (HR 2.2, 95% CI 1.5-3.2, *p* =0.019) and Allo-SCT(HR=0.149, 95%CI 0.030-0.747, *p* =0.021).

Table 4

Uni and Multivariate analysis of factors for OS

	HR (95%CI)	p	HR (95%CI)	p
Age ≥60yrs	2.346(1.494-3.683)	<0.001	1.898(1.061-3.398)	0.032
Secondary leukemia	12.034(1.266-3.270)	0.003	1.256(0.739-2.134)	0.400
WBC≥50×10^9/L	1.480(0.894-2.451)	0.127		
NPM1 mutated	0.332(0.133-0.826)	0.018	0.429(0.168-1.095)	0.077
FLT3 mutated	1.008(0.504-2.018)	0.982		
CD34+	1.195(0.698-2.047)	0.517		
Unfavorable cytogenetic/molecular risk	2.804(1.772-4.432)	<0.001	1.974(1.201-3.246)	0.007
Standard chemotherapy	2.034(1.266-3.270)	0.003	2.456(1.352-4.462)	0.003
CD200 positivity	1.431(0.873-2.346)	0.155		
CR1	0.488(0.306-0.778)	0.003	0.615(0.373-1.013)	0.056
Chemotherapy-only	2.798(1.663-4.649)	<0.001	0.452(0.105-1.943)	0.286
Auto-SCT	3.295(1.202-9.029)	0.020	0.113(0.018-0.697)	0.019
Allo-SCT	0.447(0.254-0.788)	0.003	0.149(0.030-0.747)	0.021

Abbreviations yrs years old, WBC white blood cell count,CR1 complete remission after induction therapy, Auto-SCT autologous stem cell transplantation , Allo-SCT allogeneic stem cell transplantation , chemotherapy-only repeated chemotherapy consolidation.

In subgroup analysis we further evaluated the potential impact of CD200 expression in the presence of FLT3-ITD, NPM1 wild-type(wt), intermediate cytogenetic/molecular risk, standard chemotherapy, less-intensive approaches, chemotherapy-only treatment cases. CD200 expression defined groups had no effect on DFS, but with very poor OS among less-intensive approaches,1-year OS was 53.6% (95%CI 37.2-55.2) in CD200- patients, 48%(95%CI 42.7-53.3)in CD200+ ones, and 2-year OS was 46.2%(95%CI 37.2-55.2), 29.4%(95%CI 23.4-35.5) for CD200- and CD200+(P=0.006,Fig.2). As for chemotherapy-only treatment patients, 1-year OS in CD200+ group was 35.1% (95%CI 29- 41.8), CD200-group was 42.5% (95%CI 31.1-53.9)(P=0.032, Fig.3). CD200 did not affect outcome in the subgroup with FLT3 wt (P=0.169), NPM1 wt(P=0.366) and intermediate cytogenetic/molecular risk(P=0.610), standard chemotherapy(P=0.643).

4. Discussion

Recent advances in understanding the molecular pathogenesis and prognostic markers, frontline treatment options for AML have expanded substantially in the modern era(Chen and Garcia 2020). Current therapy for AML patients emphasizes spectrum of treatment intensity and toxicity while having efficacy for more specific disease cytogenetics and mutational profiles(Zhang et al. 2019; Zhang et al. 2020). Many patients experience relapse and have unsatisfactory outcomes, and prognosis remains poor, because the treatments are not directed against leukemia stem cells (LSCs), and the cells capable of long-term self- renewal and deemed the source of relapse(Thomas and Majeti 2017). Allo-SCT is still the only curative option for AML, immune cells reconstituted from donor are capable of destroying residual LSCs, but morbidity and mortality are both high due to transplant-related side effects and refractory disease(Herbrich et al. 2021).

It was recently demonstrated that CD200 is expressed on both healthy and LSCs, the over-expression of the CD200 on AML blasts directly suppresses memory T-cell function, it can be identified as one candidate of LSC-specific immunosuppression(Coles et al. 2012; Ho et al. 2020). CD200 expression on AML has been associated with lower rates of complete remission and significantly worse overall survival in multivariable analysis(Damiani et al. 2015; Kandeel et al. 2021; Tiribelli et al. 2017; Tonks et al. 2007).In this study, we investigated the expression of CD200 on outcome of a series of 160 patients with non-promyelocytic AML. We found CD200 expression in 62.5% of cases, and is associated with CD34 positive, intermediate unfavorable cytogenetic/molecular profile, and NPM1-wild type (p <0.001, p <0.001, p <0.001, p = 0.001). Although CD200 expression was related to significant lower CR, it had no evident impact on DFS and OS in whole population. While in subgroup analysis, we found that CD200 positive in patients received less-intensive approaches, or chemotherapy-only treatment indicate poor OS.

Damiani et al. reported CD200 expression in 136/244 adult patients (56%) and found an association between CD200 expression and secondary AML (p = 0.006) and more unfavorable or favorable cytogenetic profile (p = 0.003). Furthermore, high CD200 was associated with lower CR as well as a dismal OS (p = 0.04, p = 0.02) (Damiani et al. 2015).A Data from Tiribelli et al lately also reported CD200 expression in 139/242 (57.4%) adult AML, and illstrated that CD200 expression had lower CR (p = 0.004), and it synergizes with BCL2 had markedly influence on prognosis(p= 0.009),but it alone had no impact on DFS and OS(Tiribelli et al. 2021). In our cases we did not find CD200 expression had an association with secondary, favorable cytogenetic profile and significant shorter OS as in the work by Damiani et al(Damiani et al. 2015). We found high rate of CD200 positivity in patients with unfavorable cytogenetic/molecular status($P < 0.001$), NPM1 wild type ($P = 0.001$), an association with lower rates of complete remission as recently defined by DöhnerOur and Damiani(Damiani et al. 2015; Döhner et al. 2010). Tiribelli et al lately study, focused on cytogenetically-normal(cn) AML, suggest CD200 was expressed in 67/139 (48%) cn-AML cases, indicated a lower probability of CR (OR = 2.2) and shorter survival, but CD200 expression, per se, did not impact on DFS(Tiribelli et al. 2017). In subgroup analysis, we analyzed intermediate cytogenetic/molecular status, had 30/65(46%) CD200 positive, but we did not find a negative impact on survival in intermediate status(p=0.61) as demonstrated by Tiribelli(Tiribelli et al. 2017).

Interestingly, we found CD200 worsen survival in patients received different treatment,

low-intensive approaches and chemotherapy-only treatment. Mechanisms of CD200 exerts its negative

influence on outcome is not fully defined. It was recently demonstrated that CD200 is selectively overexpressed in AML LSCs and is broadly immunosuppressive by impairing cytokine secretion in immune cell subsets, CD200+ leukemia progressed rapidly by escaping elimination by T cells in vitro(Herbrich et al. 2021) . Intensive chemotherapy and stem-cell transplantation can direct against LSC-specific antigens and eliminated residual LSCs(Ho et al. 2020).

As few data are available to evaluate impact of CD200 expression on survival outcomes in the subset of treatment-defined subgroups. Our data did not show significant poor outcomes in entire population, but demonstrated that further worsening survival in less intensive approaches and chemotherapy-only treatment subgroups. Thus, these findings suggested us to utilize intensive or novel therapeutic approaches to manipulate the immune microenvironment, reversing the escaping mechanism of CD200.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yanfang Zhang, Xi Quan, Guancheng Song, Ying Song, Shifeng Lou, Kang Zhou, Yan Shen, and Jianchuan Deng*. The first draft of the manuscript was written by* Yanfang Zhang *and* Xi Quan*. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.*

Data Availability

The datasets used in this study are available from the corresponding author on reasonable request.

Ethics approval

The patient data we used were acquired by publicly available datasets that were collected with patients' informed consent competing interests.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the all images.

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Figures

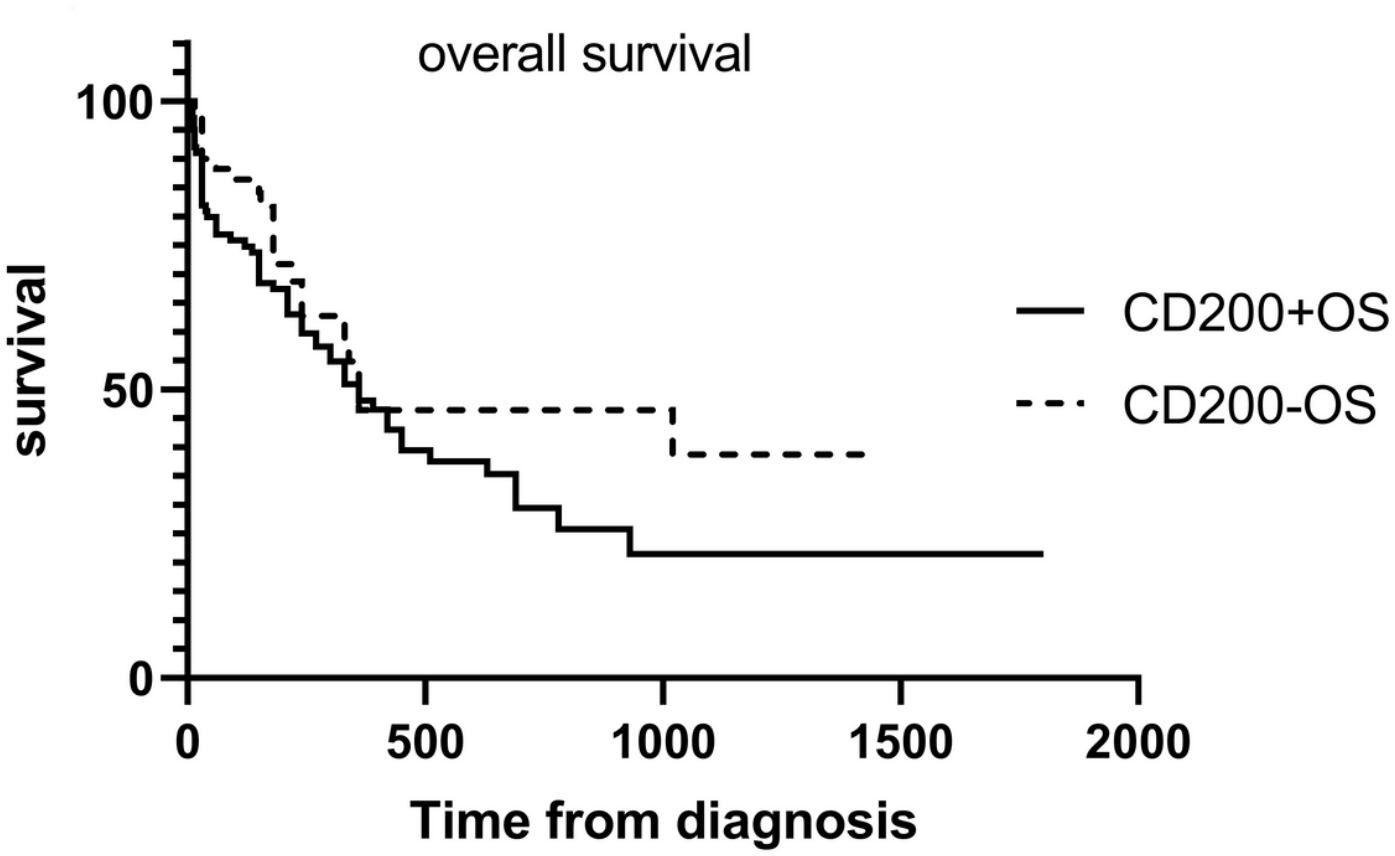

Figure 1

Kaplan–Meier estimates of overall survival (OS) in entire patients for the CD200+ versusCD200- group.

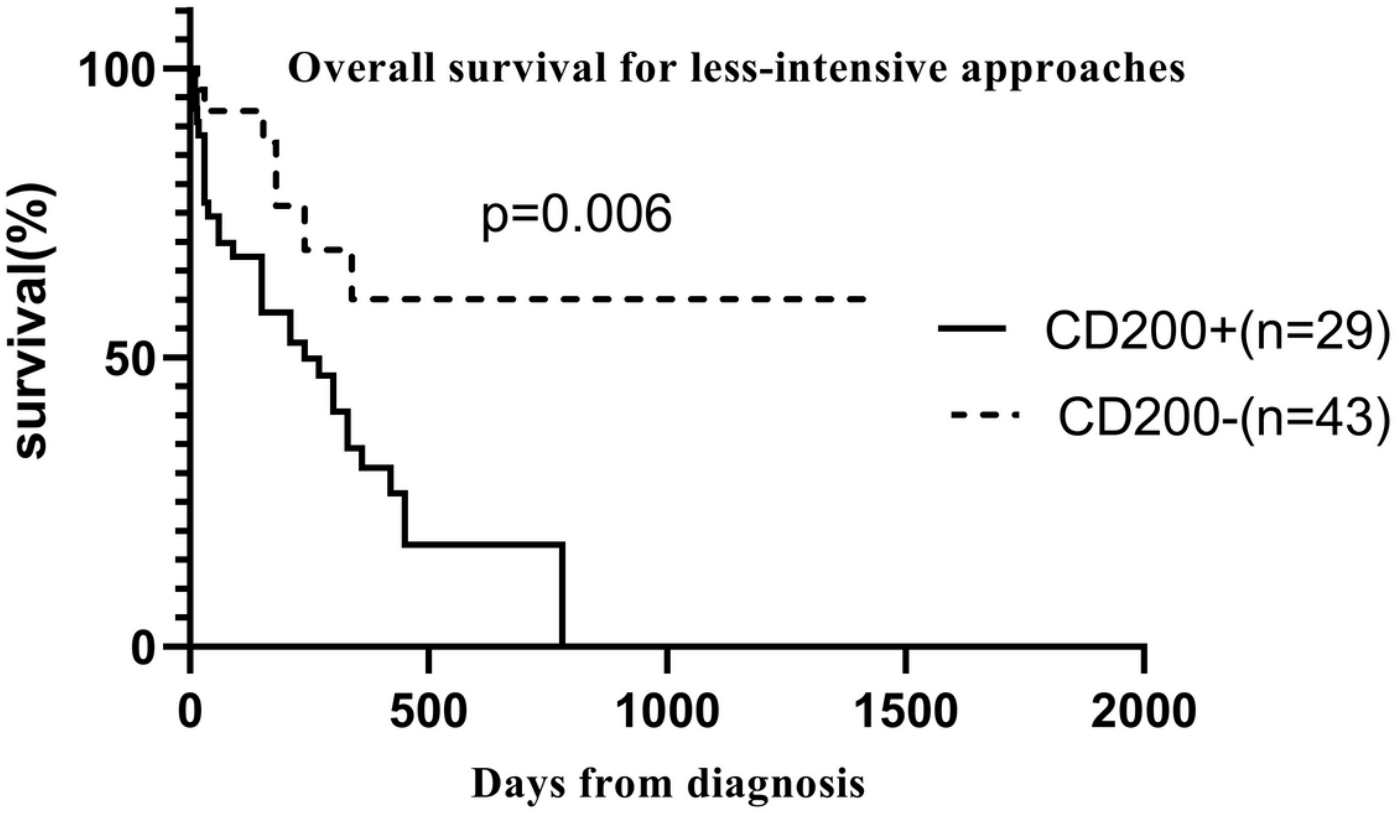

Figure 2

Kaplan–Meier estimates of overall survival (OS) in patients with less-intensive approaches for the CD200+ versus CD200- group.

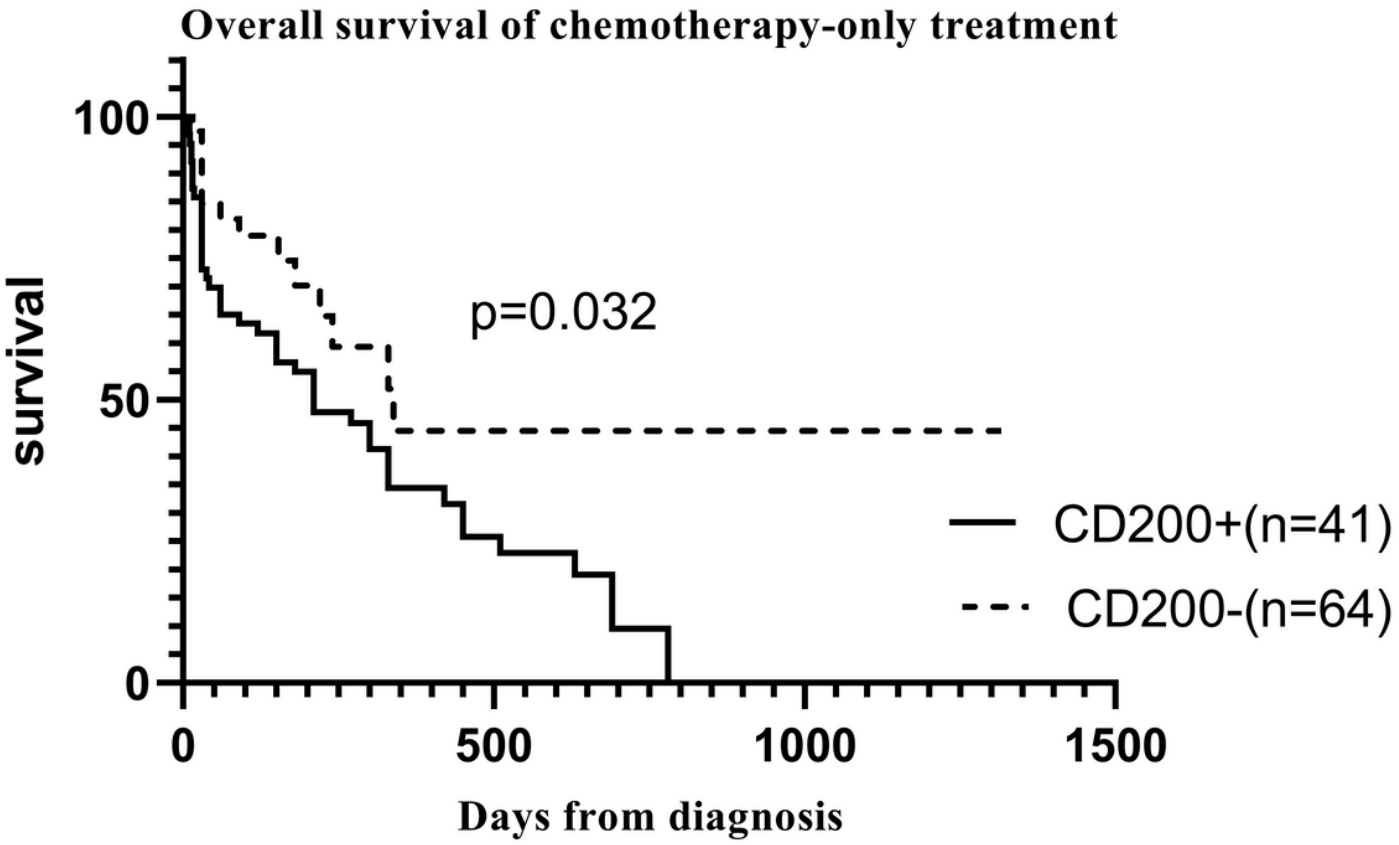

Figure 3

Kaplan–Meier estimates of overall survival (OS) in patients with chemotherapy-only treatment for the CD200+ versus CD200- group.