The influence of red blood cell transfusions on the progression-free survival of patients with localized squamous cell carcinoma of the anus treated with definitive chemoradiation

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Abstract

Background: Red blood cells transfusions (RBCT) have been associated with worse oncological outcomes in distinct tumor types. Inhibition of the activities of Natural Killer (NK) and cytotoxic T cells are the supposed mechanisms underlying a transfusion-related immune modulation. Because the impact of RBCT on the outcomes of patients with squamous cell carcinoma of the anus (SCCA) is uncertain, we aimed to evaluate its influence on the progression-free survival of patients with SCCA treated with definitive chemoradiation (ChRT).

Methodology: This was a retrospective study of consecutive SCCA patients treated with definitive ChRT. The primary endpoint was progression-free survival according to receipt of at least one unit of RBCT. Univariate and multivariate Cox regression analyses for progression-free survival were performed to evaluate prognostic factors.

Results: From February 2003 to April 2018, 136 patients were included. The median age was 59 years, 77.2% was female and 13.9% had HIV infection. Transfused patients were more frequently female and had stage III tumors. Thirty-one (22.8%) patients received a RBCT, increasing the mean hemoglobin levels from 7.6 to 8.5g/dl. With a median follow-up time of 48 months, the median progression-free survival was 36.5 versus 146.9 months for transfused and non-transfused, respectively. In the multivariate analysis, RBCT ([HR]: 6.7 [IC] 95% 3.4-13.2, p<0.001) and stage III (HR: 3.0 [IC] 95% 1.4-6.5, p =0.005) were associated with inferior progression-free survival as compared to non-transfused and stage I-II, respectively. While the rates of complete responses and persistent local disease were similar between the groups, receipt of RBCT was significantly associated with progression (69.2% versus 14.9%; p < 0.00001).

Conclusion: Our study suggests that the receipt of RBCT and clinical stage III disease were significantly associated with inferior progression free survival. RBCT or persistent anemia after transfusion did not influence the rates of complete response, but patients who received RBCT presented significantly higher rates of tumor progression.

Introduction

Non metastatic squamous cell carcinoma of the anus (SCCA) is a highly curable disease in most patients treated with definitive chemoradiation.[1] While standard 5FU and mitomycin or cisplatin combined with pelvic radiation is generally well tolerated, nearly one fourth of SCCA patients develop clinically significant anemia during treatment.[2] Hemoglobin count below 12g/dL has been associated with inferior responses among patients with SCCA treated with chemoradiation.[2] To minimize this, some of these patients may need blood transfusions to compensate them clinically and/or to improve the antitumor effects of radiation. However, the receipt of blood transfusions have been associated with worse prognosis in patients with different types of cancers.[3,4] Inhibition of the activities of Natural Killer (NK) cells and cytotoxic T cells are the supposed mechanisms underlying a transfusion-related immune modulation.[5] Moreover, this effect in cellular elements can be worsened by a prolonged storage time of

hematological products and the accumulation of bioactive substances and cell fragments in stored red blood cells (RBCT).[6, 7, 8] These immunomodulatory mechanisms were hypothesized to diminish immune-surveillance and potentially increase cancer recurrence.

The putative immunosuppressive effect of blood transfusion was initially described in 1973 in patients who underwent renal transplantation with cadaver kidneys, when less graft rejection was documented among transfused patients.[9] At that time, RBCT became one of the treatment strategies to improve kidney engraftment following renal transplantation.[9] Yet, the receipt of RBCT was later linked to increased disease recurrence and metastases among patients who had a resected cancer,[10] and was an independent factor for morbidity and mortality.[11,12,13] The first reports associating RBCT with higher risk of cancer recurrence were observed among patients undergoing resection of colorectal tumors.[12] Following the universal practice of blood filtration implemented in 1990 in Europe, it was believed that the immunosuppressive effects associated with transfusions would be eliminated, since donor leukocytes, considered the probable agent causing immunosuppression, would be eliminated.[14] Nevertheless, there are still debates about how much filtration minimizes the negative effects of transfusion with unmodified or modified blood, autologous transfusions and non-transfused patients.[15,16]

The risk of SCCA significantly increases with immunosuppressive conditions. A nationwide Danish study demonstrated higher standardized incidence ratios of SCCA among HIV-infected patients, solid organ recipients, those with hematological malignancies and autoimmune illnesses[17]. Also, our group observed that HIV-infected patients with localized SCCA experience inferior disease-free survival rates[18], significant longer time to achieve local complete response[19] and, among metastatic patients, those with HIV-infection present numerically inferior median overall survival.[20] We hypothesized that immunomodulatory effects associated with filtered and irradiated RBCT could also influence the prognosis of patients with SCCA treated with definitive chemoradiotherapy (ChRT).

Patients And Methods

Retrospective comparative cohort study of patients with localized SCCA who were treated at the Ac Camargo Cancer Center, a large comprehensive cancer center located in the city of Sao Paulo, Brazil. All consecutive SCCA patients treated with curative-intent ChRT from February 2003 to April 2018 were included and divided into two groups: patients who received at least one unit of RBCT during, 30 days before, or up to 30 days after the end of ChRT, and patients who were not transfused. Patients with stage IV disease at diagnosis, those who did not receive cisplatin and 5-FU (5-fluorouracil/capecitabine or mitomycin C and 5-FU/capecitabine with concomitant radiotherapy (RT) or who were seen at the institution only for a second opinion were excluded. The period from 2003 to 2018 was selected due to the adequate availability of information on blood transfusions based on the registration of our blood bank.; the 2018 year was selected as the time limit to allow for a minimum of two years follow up after ChRT to allow enough time to measure disease recurrence. All transfusions were filtered and irradiated on

the first day of collection and pre-storage, and collected with Fresenius Kabi quadruple packet kits, with anticoagulant SAG-MANITOL, by top and bottom systems.

The primary endpoint was progression-free survival, as a time-to-event variable, according to receipt of RBCT, which was compared between groups and evaluated in an adjusted analysis for other potential prognostic factors. Other endpoints were progression-free survival rates overall and within 12 months of ChRT, rates of complete response/persistent tumor, frequency and severity of anemia according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0), reasons for RBCT and description of clinical features of transfused patients compared to those not transfused.

The following clinical data were collected from electronic medical records: age at the start of ChRT, sex, tumor stage at diagnosis according to the 8th edition of the American Joint Committee on Cancer, pre-treatment ECOG, type of chemotherapy (cisplatin or mitomycin combined with a fluoropyrimidine), result of HIV serology (if not described, we considered it as negative since HIV serology testing is part of our local guideline), receipt of RBCT, blood group of patients who received transfusion, clinical indication of transfusion, pre-treatment hemoglobin, the increase in hemoglobin after transfusion (considering the first laboratory examination after receiving the blood unit), recurrence or persistence of SCCA identified in clinical examination and confirmed by biopsy and/or disease at a distance identified by imaging exams, dates of complete response if this was achieved, and dates of local/distance recurrence.
The study was approved by our local Ethics Committee.

Population characteristics were summarized by descriptive statistics. Comparisons between independent groups were made by the chi-square test for categorical variables, and by the Mann-Whitney test, for continuous variables. Progression-free survival was calculated from the end of chemoradiotherapy until clinical/radiological local or distant recurrence, locoregional progression or death from any cause and was reported by the Kaplan Meier estimator. The median follow-up time was estimated by the reverse Kaplan-Meier method. To adjust for confounders, other prognostic factors for progression after definitive ChRT were tested in univariate and multivariate Cox regression models: clinical stage (I and II versus III), receipt of at least one RBCT, and presence of HIV infection. Analyses were all case-complete. Values of $p < 0.2$ were considered significant for univariate analyses and for multivariate analyses, $p < 0.05$. All analyses were performed by the SPSS software version 25.

Results

From February 2003 to April 2018, 183 patients with SCCA were identified. We excluded 18 patients in stage IV at diagnosis, 17 patients treated with non-standard ChRT protocols and 12 who were seen in a second opinion consultation. The characteristics of the study population of 136 patients are summarized in Table 1, according to receipt of RBCT.

Table 1
Characteristics of eligible patients

Characteristic	Transfused	Not Transfused	P values
Number of patients	31 (22.8%)	105 (77.2%)	
(136 = 100%)			
Age (median, range)	59 (33–88)	59 (33–88)	0.23[#]
Gender			
Female	27 (87.1%)	78 (74.3%)	0.020[##]
Male	4 (12.9%)	27 (25.7%)	
Race			
Caucasian	28 (90.3%)	82 (78.1%)	< 0.00001[##]
Mixed African	3 (9.7%)	22 (21%)	
Black	0	1 (0.9%)	
Type of chemotherapy*			
FU Mitomycin C	21 (67.7%)	78 (74.3%)	0.34[##]
FU Cisplatin	10 (32.3%)	27 (25.7%)	
State (AJCC 2017)			
I	1 (3.2%)	11 (10.4%)	0.00019[## $]
II	8 (25.8%)	47 (44.8%)	
III	22 (71%)	47 (44.8%)	
ECOG			
0	15 (48.4%)	69 (65.7%)	0.044[## $$]
1	13 (41.9%)	33 (31.4%)	
2	3 (9.7%)	2 (1.9%)	
3	0	1 (1%)	
HIV-infection			
Positive	3 (9.7%)	16 (15.2%)	0.28[##]
Negative	28 (90.3%)	89 (84.8%)	

**5-FU: Fluorouracil ** RBCT: red blood cell transfusion.* RBCT: red blood cell transfusion [#] Mann Whitney test; [##] Chi-Square test; [$]: stages I and II versus III; [$$] 0 and I versus 2 and 3.

Characteristic	Transfused	Not Transfused	P values
Transfused			
RBCT** (median, range)		2.8 (1–8) units	
Pre-transfusion laboratory (average, range)		7.6 g/dl (6-9.1)	
Post-transfusion laboratory (average, range)		8.5 g/dl (7-12.8)	
Transfusion moment			
After treatment, within 30 days		10 (32.3%)	
During treatment		17 (54.8%)	
Before treatment, within 30 days		4 (12.9%)	

** 5-FU: Fluorouracil ** RBCT: red blood cell transfusion.* RBCT: red blood cell transfusion [#] Mann Whitney test; [##] Chi-Square test; [$]: stages I and II versus III; [$$] 0 and I versus 2 and 3.

Median age was 59 years, more than 70% was female and received the Nigro regimen and 13.9% had HIV infection. When compared to non-transfused patients, those who received at least one unit of RBCT were more commonly female ($p = 0.20$), Caucasian ($p < 0.00001$), had clinical stage III tumors ($p = 0.00019$), and baseline ECOG performance status of 2 or higher ($p = 0.044$).

There were 50 transfusion requests: 16 (32%) patients with grade 2 anemia, and 29 (58%), with grade 3 anemia, and 5 cases were unclassified because they had no record of hemoglobin pre-transfusion. Most patients received RBCT during ChRT. The causes of anemia were bleeding in 15 (30%) cases, considered to be secondary to ChRT in 21(42%), clinical compensation prior to ChRT in 9 (18%) patients with symptomatic anemia and 5(10%), due to surgical procedures. Thirty-one (22.8%) patients were transfused, and the mean pre- and post-transfusion hemoglobin was 7.65 g /dl (range 6-9.1g/dl) and 8.50 (7-12.8g/dl), respectively, with an average increase of 0.9 g/ dl hemoglobin per patient after transfusion.

Table 2 depicts patterns of progression and response according to receipt of RBCT. While the rates of complete responses and persistent local disease are similar between the two groups, patients who received RBCT experienced significantly more disease recurrences (69.2% versus 14.9%; $p < 0.00001$).

Table 2
Relapse and persistent disease after complete treatment

	Transfused	Not transfused
All 136 (100%)	31 (100%)	105 (100%)
Rate of complete responses	26 (83.9%)	87 (82.9%)
Lasting response	8 (30.8%)	74 (85.1%)
Relapse or progression	18 (69.2%)	13 (14.9%)
Persistent disease	5 (16.1%)	18 (17.1%)

In a median follow-up of 48 (6–84) months, 36 (26.5%) out of 136 patients presented disease progression: 17 (47.2%) within one year of definitive treatment and 19 (52.7%) within 7 years of the end of treatment. The median progression-free survival of the whole cohort was 120 months and the rate of progression-free survival at one year from ChRT was 88.9%. The median progression-free survival was 36.5 versus 146.9 months for patients who did and who did not receive RBCT ($p < 0.01$), respectively. Table 3 shows the results of the univariate and multivariate analyses for factors potentially associated with progression-free survival. The multivariable analysis identified that patients who received RBCT presented a 6.7 times ([HR]: 6.7 [IC] 95% 3.4–13.2, $p < 0.001$) higher risk of progression when compared to those who did not receive RBCT; stage III patients presented 3.0 times ([HR]: 3.0 [IC] 95% 1.4–6.5, $p = 0.005$) higher risk of progression when compared with staging I or II; the small number of HIV-positive patients precluded the insertion of this variable in the analyses.

Of the 22 patients who received RBCT, disease progression was evident in locoregional or paraaortic lymph nodes (10), locally (3), lungs (1), liver (3), vulva (1) and peritoneum (1). Among the 14 patients who did not receive RBCT, disease progression occurred in lymph nodes (7), peritoneum (2), bone (1) and locally (3).

Table 3
– Cox regression for disease-free survival

	Univariate			Multivariate	
	Nº	**HR (95%CI)**	P	**HR (95%CI)**	P
Parameters					
Receipt of RBCT At least one	22	7.5[3.8–14.7]	<0.001	6.7[3.4–13.2]	< 0.001
Not transfused (referent)	14	1		1	
Clinical stage:					
III	27	3.7[1.7–7.8]		3.0[1.4–6.5]	
I and II (referent)	9	1	0.001	1	0.005

Discussion

Blood transfusion has been associated with worse clinical outcomes in patients with various malignancies.[3,11,12,16] Inflammatory cells and red cell elements transfected during blood transfusion can mediate an immunosuppression effect leading to impaired immune surveillance and increase risk of tumor progression. [3,11,12,16] In the present study, we found that receiving at least one RBCT significantly increased the risk of disease progression among SCCA patients undergoing definitive ChRT. While transfused patients more frequently had stage III tumors and ECOG performance status 2 or higher, the receipt of RBCT was associated with a 6.7 times higher risk of progression, independently of clinical stage. Additionally, despite the similar rates of persistent tumors after ChRT in both groups, transfused patients experienced nearly 4.5 times more disease recurrences after complete response. Patients who received RBCT maintained anemia, and this may have contributed to inferior oncological outcomes.

Several retrospective studies observed the associations between blood transfusion (mostly red blood cells) and increased rates of bacterial infections after curative resection of colorectal cancer (CRC), with subsequent increased postoperative mortality.[11,12,13] Because such higher mortality may reflect higher tumor stage and/or comorbidities, it is unknown whether RBCT is a true prognostic factor or just a confounder for overall survival and morbidity after surgery. Therefore, studies evaluating CRC recurrence following RBCT have been conducted to avoid such confounding. And again, receipt of RBCT was linked to decreased disease-free survival time and high tumor recurrence rates in CRC, pointing to a possible causal effect involving unfiltered red cells, which are overloaded with immunomodulatory leucocytes of donors.[15,16]

The hypothesis that blood transfusion can induce immunosuppression was seen in early studies with renal transplant.[9] In fact, transfusion of stored blood was found to be an effective immunosuppressive

method after kidney transplant from unrelated donors. Nowadays, the better understanding and modulation of the immune system resulted in great advances in the treatment of many neoplasms. We previously demonstrated that HIV infection resulted in worse prognosis in patients with locally advanced SCCA.[18] As a result, it is believed that immune surveillance plays an important role in combating SCCA tumor cells.[17]

Anemia is a frequent adverse event during chemotherapy and is associated with poor prognosis.[2] Our two groups were similar in terms of type of chemotherapy regimen utilized, with approximately 23% rates of grade 3 or 4 anemia, which is similar to that reported by randomized trials of SCCA managed by ChRT.[21] Decreased red blood production is not solely the result of myelotoxicity but it may also reflect a compromised clinical condition and patient frailty. In fact, in our study patients who received RBCT more frequently presented stage III tumors and had an ECOG *performance status* 2 or higher. Yet, receipt of RBCT was an independent risk factor for disease progression in the multivariable analyses.

It is also possible that persistent anemia after RBCT was a contributing factor that impaired treatment efficacy. In fact, the mean hemoglobin level of the transfused patients was 7.2 g/dl and was elevated to only 8.5 g/dl during treatment – likely because of myelosuppression of ChRT. Based on these results we can conclude that most patients received ChRT with low hemoglobin levels. The best cut-off levels for hemoglobin prior to ChRT for SCCA has not been determined. A multicenter study conducted in Italy, with 161 SCCA patients treated with ChRT showed that the chance of obtaining a complete response was increased by 5.6% for each g/dl in patients with hemoglobin equal to or greater than 11 g/dl up.[22] In contrast, another retrospective study found no association between anemia and response to ChRT in SCCA.[2] While it is possible that the immunosuppressive effects of RBCT plus persistent anemia both contributed to inferior progression free survival among transfused patients, we did not observe differences in complete response rates according to receipt of RBCT, which were more than 80% in both groups. Interestingly, the rates of progression, after complete response, were significantly higher among transfused patients, pointing to a later, rather than an acute, effect on the risk of cancer recurrence. Therefore, it seems that persistent anemia in the transfused group did not influence response to ChRT. Another possible explanation for worse progression free survival following RBCT is that patients who required RBCT were frailer and needed more treatment-interruptions. Unfortunately, we could not retrieve information of ChRT dose-intensity, an important known prognostic factor for progression.[23]

Our study has some relevant limitations. As a retrospective analysis, it was not possible to prove causality between RBCT and SCCA progression after ChRT. The number of HIV-infected patients who received RBCT was too small, what prevent us from testing this known prognostic factor in the multivariable analyses. Could not retrieve information on dose-intensity of ChRT, a known and important prognostic factor for localied SCCA.[23] Also, the slow increment of hemoglobin levels after RBCT, possibly induced by myelossupression from ChRT, might have confounded (or contribute to) higher progression rates among transfused patients.

Prospective studies are the only way to better evaluate causality between RBCT and cancer recurrence or progression. The prospective evaluation of immune serum markers prior and after RBCT could measure whether (and to which extent) the transfusion of filtered and irradiated pre-storage blood leads to an increase in serum markers associated with immunosuppression. Additionally, detailed analyses of pre-transfusion red cell storage conditions (time, temperature) are important to measure cellular and humoral changes associated with RBCT. However, prospective studies are hard to be performed in this context because other confounders may be associated with immunomodulation, such as concomitant receipt of chemotherapy and radiation, the concurrent diagnosis of cancer, and the intrinsic selection bias, since patients who require RBCT may themselves be at higher risk of tumor progression for unknown biological reasons.

Conclusion

Despite the limitations of retrospective designs, our study suggests the receipt of RBCT, even after undergoing the pre-storage filtration process, and higher clinical stage were independently associated with higher risk of disease progression among patients with SCCA treated with curative-intent ChRT. The receipt of RBCT or persistent anemia after transfusion did not influence the rates of complete response, but patients who received RBCT presented significantly higher rates of tumor progression.

Declarations

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Conflicts of interest of authors

none to declare

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The study was reviewed and approved by institutional ethics committee - registration number 2616/18

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