Use of Blood Products in Patients Treated Surgically for Stage I Non-Small Cell Lung Cancer

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OBJECTIVE: Retrospective study on the relation between the use of blood products and survival rates in patients treated surgically for stage I non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS: The study included 856 patients who underwent surgical resection from 1969 to 2000 for stage I NSCLC, classified histologically according to the current guidelines of the Spanish Society of Pulmonary and Thoracic Surgery (SEPAR). Patients who died in the postoperative period were excluded from the study. A series of clinicopathological variables were recorded, including the perioperative use or not of blood products. Descriptive, univariate, and multivariate statistical analyses were performed. Follow up concluded in December of 2003.

RESULTS: One hundred twenty-five patients (14.6%) underwent a perioperative transfusion. A significant association was found between the use of blood products and tumor size (*P*<.001), pneumectomy (*P*<.001), and cell type (*P*<.05). The respective 2, 5, and 10-year survival rates were 78%, 63%, and 54% for the nontransfusion group, and 73%, 59%, and 46% for the transfusion group. Both survival curves were compared and no significant differences were found (*P*=.23). Multivariate regression analysis included tumor size, patient age, and histologic cell type (squamous cell carcinoma or not); no relation between transfusion and survival was found.

CONCLUSIONS: In our series, we found no difference in survival rates for patients with stage I NSCLC after perioperative blood transfusion.

Key words: *Bronchogenic carcinoma. Stage I. Surgery. Transfusion.*

Estudio del uso de hemoderivados en el carcinoma broncopulmonar no anaplásico de células pequeñas en estadio I sometido a tratamiento quirúrgico

OBJETIVO: Estudio retrospectivo sobre la influencia del uso de hemoderivados en la supervivencia del carcinoma broncopulmonar no anaplásico de células pequeñas (CBNACP) en estadio I sometido a tratamiento quirúrgico.

PACIENTES Y MÉTODOS: Se incluyó en el estudio a 856 pacientes (1969-2000) diagnosticados de CBNACP, que se resecaron y clasificaron como estadio I patológico según la actual normativa SEPAR, y se excluyó la mortalidad postoperatoria. Se recogieron una serie de variables clinicopatológicas, incluida la utilización o no de hemoderivados en el perioperatorio, y se aplicaron análisis estadísticos descriptivos, univariante y multivariante. El seguimiento finalizó en diciembre de 2003.

RESULTADOS: En el perioperatorio se transfundió a 125 pacientes (14,6%). La utilización de hemoderivados se relacionó significativamente con el tamaño tumoral (p < 0,001), la realización de una neumonectomía (p < 0,001) y el tipo histológico (p < 0,05). La supervivencia fue del 78, el 63 y el 54% a los 2, 5 y 10 años, respectivamente, para el grupo de pacientes no transfundidos, y del 73, el 59 y el 46% para el grupo de transfundidos. La comparación de ambas curvas de supervivencia no mostró diferencias significativas (p = 0,23). En el análisis multivariante entraron en regresión el tamaño tumoral, la edad y la variedad histológica epidermoide/no epidermoide. En este análisis no se demostró ninguna relación de la transfusión con la supervivencia.

CONCLUSIONES: No se ha encontrado, en nuestra serie, ninguna variación en la supervivencia del CBNACP en estadio I tras el uso de hemoderivados en el perioperatorio inmediato.

Palabras clave: *Carcinoma broncogénico. Estadio I. Cirugía. Transfusión.*

Introduction

A large number of studies have investigated the influence of transfusion of blood products on survival among patients who undergo a variety of surgical procedures. Ever since early studies reported better prognosis for renal transplant patients undergoing frequent transfusions,[1,2] investigators have considered the possibility that immunosuppression resulting from such transfusions might be partly responsible for this improvement. Immunosuppression that contributes to this beneficial effect in transplantation could, however, be counterproductive in other diseases such as cancer, in which tumor growth and metastasis would be favored. In view of findings from studies of colon cancer and breast

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Manuscript received September 30, 2004. Accepted for publication January 1, 2005.

cancer, authors such as Tartter et al[3] designed studies to analyze the influence of perioperative transfusion on lung cancer. Since then, a number of studies have also aimed to investigate the influence of transfusion on prognosis for non-small cell lung cancer (NSCLC) treated surgically, but despite the long period over which such studies have been appearing, conflicting results are still reported—some studies show an unfavorable influence,[3-8] whereas as others find no variation.[9-13]

The objective of this study was to assess the influence on survival of these therapeutic procedures in our patients, who were limited to those with the disease in its initial phases and who had a longer life expectancy, that is, to those with stage I NSCLC.

Patients and Methods

Between January 1, 1969 and December 31, 2000, 856 patients with stage I NSCLC, according to the guidelines published by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR),[14] underwent surgery in the thoracic surgery department of the Hospital Universitario La Fe in Valencia, Spain. No patient received additional cancer treatment besides surgery. The series did not include patients who died during the perioperative period.

A set of clinical, pathological and time variables were retrospectively analyzed. These variables were sex, age, preoperative symptoms, time between diagnosis and operation, tumor site (central or peripheral, left or right, and in the bronchial tree), characteristics of surgical resection (size, whole or partial, typical or atypical), histologic type, extent of invasion and tumor size, units of blood products transfused, date of surgery, and date of death.

The surgical procedure consisted of resection of the lung, provided no functional limitation was present. Lymph nodes were not systematically dissected; lymphadenectomy was performed as needed according to the macroscopic findings. Histologic typing was done in accordance with the guidelines published by the World Health Organization in 1999.[15] No patient underwent autologous transfusion. Whole blood or packed red blood cells were used, and transfusion was done according to the criteria defined by the blood therapy committee of the hospital. Thus, before the procedure, normovolemic patients with high cardiopulmonary or vascular risk received a transfusion to maintain hemoglobin above 8 g/dL. During the procedure, transfusion decisions were based on assessment of blood volume and hemoglobin according to losses, hemodynamic function, and initial hemoglobin levels. In the postoperative phase, normovolemic patients with no signs of active bleeding received a transfusion if hemoglobin levels dropped below 7 g/dL, provided there were no other risk factors, such as age greater than 70 years or obvious clinical symptoms of anemia.

Mean (SD) duration of follow-up of the patients was 17.39 (0.66) years, and the study ended on December 31, 2003.

Statistical Analysis

Statistical treatment of the data comprised an initial descriptive part and a second comparative or inferential part. The χ^2 test and the Student *t* test were used to compare the transfusion variable with the other variables. The Kaplan-Meier method was used to calculate the probability of survival and the survival curves were compared by a log-rank test.[16] The Cox proportional hazards model was used for the multivariate analysis,[17] which included only variables that were significant in the univariate analysis ($P \leq .1$).

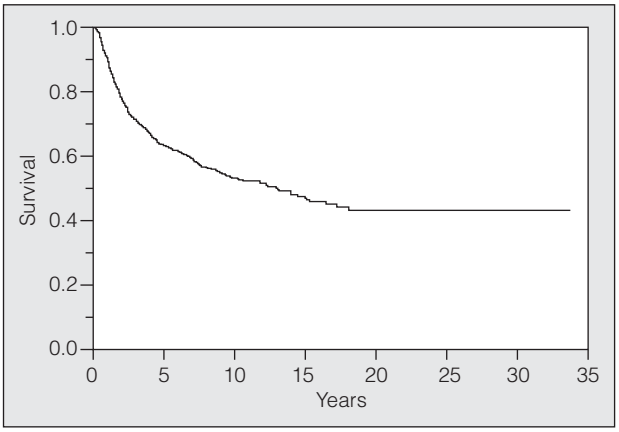

Figure 1. Overall survival for the series.

Results

Overall survival for the series was 63.35% after 5 years and 53.27% after 10 years (Figure 1). In the overall population, 808 were men (94.4%) and 48 were women (5.6%). Mean age was 62.07 (8.95) years (range, 30-87 years). The tumor was discovered by chance in 287 patients (33.5%), whereas 569 patients (76.5%) were symptomatic. Pneumonectomy was necessary in 191 patients (22.3%) and 665 (77.7%) required partial resection. According to the histologic findings, 555 patients (64.8%) had squamous cell carcinoma and 301 had other types of carcinoma (220 patients had adenocarcinoma and 81 large-cell carcinoma). The mean tumor size was 4.59 (2.23) cm (range, 0.1-15 cm).

TABLE 1
Correlations According to the χ^2/Student *t* Test*

Variable	Nontransfused (n=731; 85.4%)	Transfused (n=125; 146%)	*P*
Sex			
Men	688 (80.30)	120 (14.01)	NS
Women	43 (5.02)	5 (0.58)	
Age, years†	61.97 (8.95)	62.65 (9.01)	NS
Preoperative symptoms			
Asymptomatic	253 (29.55)	34 (3.97)	NS
Symptomatic	478 (55.84)	91 (10.63)	
Stage			
IA	149 (17.40)	19 (2.21)	NS
IB	583 (68.10)	106 (12.38)	
Histology			
Squamous cell carcinoma	466 (54.43)	89 (10.39)	.04
Adenocarcinoma	199 (23.24)	21 (2.45)	
Large-cell carcinoma	66 (7.71)	15 (1.75)	
Tumor diameter, cm†	4.43 (2.10)	5.45 (2.75)	<.001
Type of surgery			
Pneumonectomy	147 (17.17)	44 (5.14)	<.001
Partial resection	584 (68.22)	81 (9.46)	

*NS indicates not significant. Data are expressed as number of patients (%) unless otherwise indicated.
†Data expressed as mean (SD).

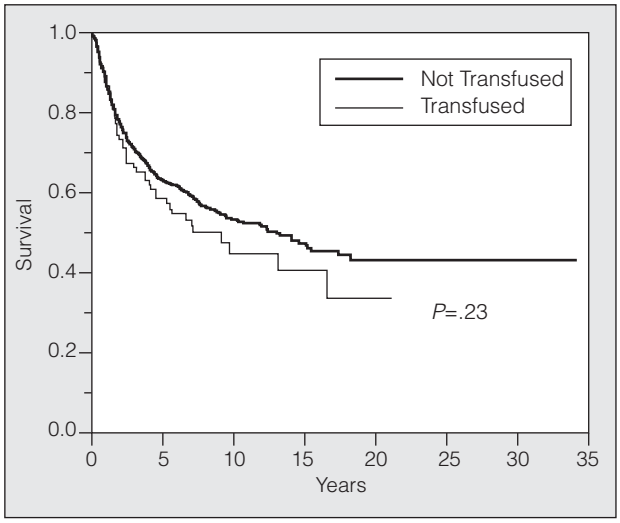

Figure 2. Survival according to whether or not patients received transfusion.

Blood transfusions were required by 125 out of 856 patients (14.6%). Twenty-six of those who underwent transfusion of blood products received a single unit, 54 received 2 units, and 45 received 3 or more units (mean, 3.48 [4.65] units; range, 1-35 units). The values of the variables analyzed are presented in Table 1 by whether or not patients received a transfusion, along with the statistical significance of the differences.

Survival, estimated with the univariate analysis according to whether or not blood products were transfused, was 78% after 2 years, 63% after 5 years, and 54% after 10 years for nontransfused patients, and 73%, 59%, and 46% after the same periods, respectively, for the transfused group. Comparison of

TABLE 2
Variables and Survival: Univariate Analysis

Variable	No. of Patients	5-Year Survival, %	*P*
Sex			
Men	808	63	.4911
Women	48	51	
Age, years			
<60	356	68	.0165
>60	500	69	
Symptoms			
Asymptomatic	287	68	.0332
Symptomatic	569	60	
Site			
Right	457	63	.8683
Left	399	62	
Resection			
Partial	665	62	.4582
Pneumonectomy	191	63	
Histology			
Squamous cell carcinoma	555	66	.0287
Other carcinomas	301	56	
Size, cm			
<3	268	76	
3.1-5	333	61	<.0001
>5	255	50	
Tumor			
T1	167	76	.0004
T2	689	59	
Transfusion			
No	731	63	.2386
Yes	125	59	

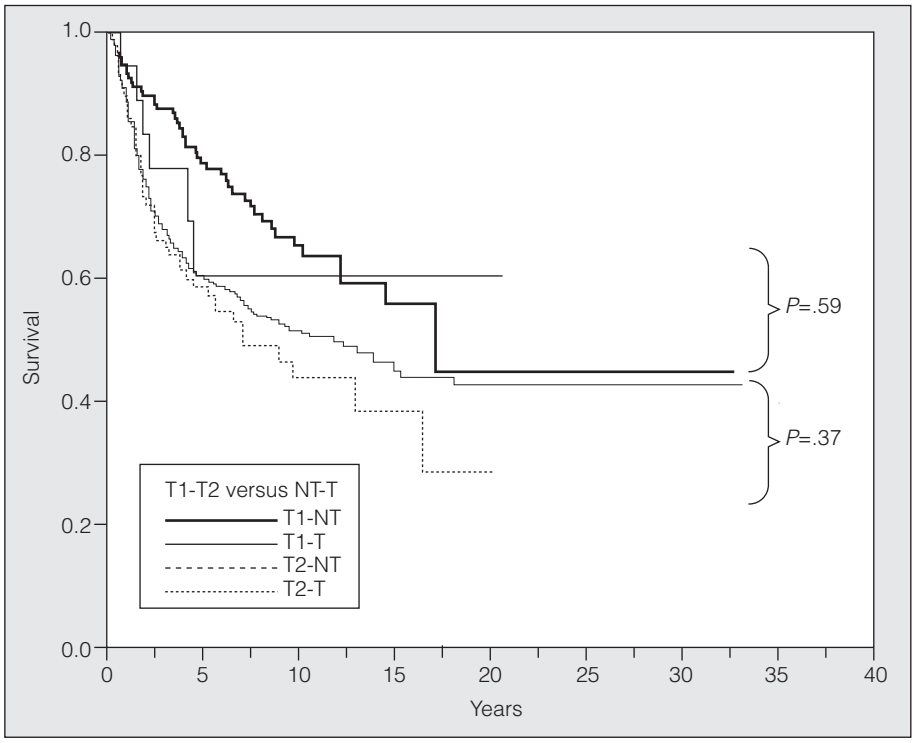

Figure 3. Survival for T1 and T2 tumors versus transfused (T) and nontransfused (NT) patients.

the 2 survival curves showed no significant differences (*P*=.23) (Figure 2). Analysis of survival according to transfusion and whether populations were classified as T1 or T2 also showed no effect on prognosis (Figure 3). Likewise, survival among patients whose cause of death was directly attributed to cancer did not vary according to whether transfusion was done or not (Figure 4). The remaining variables analyzed are shown in Table 2.

Multivariate regression analysis included tumor size, patient age, and histologic cell type (squamous cell or other carcinomas); no relation between transfusion and survival was found (Table 3).

Discussion

Blood transfusions are relatively common in the perioperative period of certain surgical procedures, and particularly in oncological surgery. No one doubts the immediate beneficial effect of transfusions but the practice is questioned because long-term side effects may worsen the prognosis. Such long-term effects have been suggested in light of the observed immunosuppression in patients undergoing to kidney transplantation who receive frequent transfusion of blood products.[1,2]

Immunosuppression in a disease such as cancer would, in principle, be expected to have an unfavorable effect, and so a series of studies were undertaken to investigate the influence of perioperative transfusion on a variety of cancers. Despite the large number of studies appearing in the literature over a long period of time, a clear relationship between transfusion and shorter survival has not been demonstrated. Meta-analyses show that the findings of these studies are contradictory and conclude that evidence for a causal relationship is lacking.[18-20]

In this retrospective study, we analyzed a population with NSCLC in its initial phase in an attempt to avoid the many factors associated with survival in cancer in advanced stages.[4,5,10,11,13,21,22] No differences in survival were observed between transfused and nontransfused patients, even when the 2 subgroups of stage 1 (T1N0 and T2N0) or the subgroup of patients who died of cancer were considered independently.

Studies that concentrate on stage 1 NSCLC show a variety of findings. Our findings agree with those of some studies, such as that of Pastorino et al,[9] but completely contradict those of other studies.[6] One of the studies that disagrees with ours is that of Nosotti et al,[8] who prospectively evaluated only patients with stage 1 NSCLC who underwent lobectomies to ensure that the population was as homogeneous as possible. That study showed statistically significant differences in both the univariate and multivariate analyses, with prognosis appearing worse when leukocytes were present among the blood products transfused. The authors therefore reflected on whether transfusions of blood products without leukocytes would be cost-effective.

Other authors have reported a correlation between the need for transfusions during the perioperative period and pneumonectomy, as was observed in our study

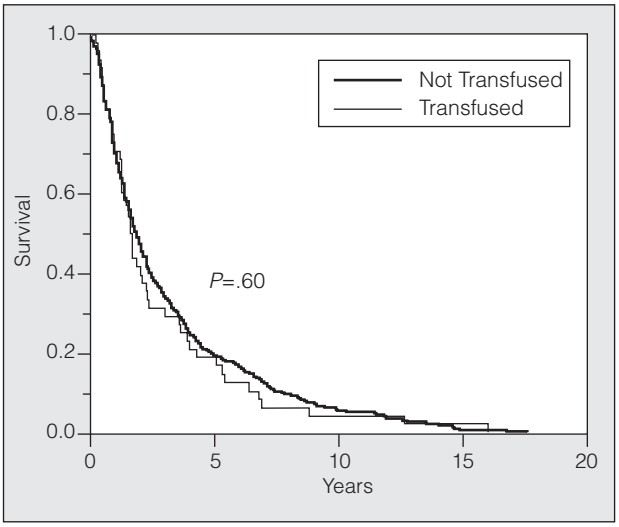

Figure 4. Survival among patients who died of cancer according to whether or not they received a transfusion.

(*P*<.001).[10,13] These studies did not, however, find significant correlations between the need for transfusion and tumor size or histologic type, unlike our study where these correlations were significant (*P*<.001 and *P*=.04, respectively). Such a relationship would be expected, regardless of the variables analyzed in each

TABLE 3
Multivariate Analysis

Variable	Regression Coefficient	*P*
Size	0.118	<.001
Age	0.018	.004
Histologic type	0.256	.021

Risk is calculated as size ×0.118+age ×0.018+histologic type ×0.256. Size is expressed in centimeters; age in years. For histologic type, squamous cell carcinoma = 1, and other carcinomas = 2.

TABLE 4
Literature Review of Patients Who Needed Transfusion of Blood Products

Author	Transfusion, %	Population
Tratter et al[3]	35.7	T1-T2 N0
Hyman et al[4]	31.4	Stage I-II (TNM 1978)
Pastorino et al[9]	55	T1-T2 N0
Keller et al[10]	39	Stage I-II (TNM 1986)
Moores et al[5]	51.2	Stage I-II-III (TNM 1986)
Wu[24]	56.6	T1-T2 N0
Little et al[6]	49.5	T1-T2 N0
Pena et al[11]	23.6	T1-T2 N0
Gwin and Keller[25]	18.3	T1-T2 N0
Zimmermann et al[26]	53.1	
Hallfeldt et al[27]	30*	
Novak et al[12]	59.4	
Rainio et al[21]	33.9	Stage I-II-IIIA (TNM 1986)
Casanova et al[13]	48.3	Stage I-II-IIIA (TNM 1997)
Dougenis et al[23]	16.1	Stage I-II-III-IV (TNM 1997)
Nosotti et al[8]	24.5	T1-T2 N0
Rzyman et al[22]	66.9 (29.4*)	T1-T2 N0
Our study	14.6	T1-T2 N0

*Autologous transfusion.

study, as both large tumors and those exhibiting the most extensive regional spread tend to require a pneumonectomy. Surgery in such cases is more aggressive and loss of blood volume associated with removal of the organ is greater. However, survival in our series was not significantly associated with whether or not pneumonectomy was practiced (*P*=.45).

Finally, the high percentage of patients who require transfusion of blood products in the studies reported in the literature is noteworthy[3-6,8-13,21-27] (Table 4), whereas transfusion was needed by only 14.6% of our patients. Our findings are consistent with those of Dougenis et al,[23] who reported that 16.1% required transfusions. Those authors suggested that the selection criteria before, during, and after the operation should be stringent to avoid unnecessary transfusions, which not only might increase immunosuppression but also posttransfusion reactions. Transfusion may also be a vehicle for dangerous infections such as hepatitis and the human immunodeficiency virus. In their prospective study, Dougenis et al propose a series of guidelines for avoiding the side effects of preoperative amenia. Thus, the authors recommend an initial study of preoperative comorbidity, careful attention to techniques to foster hemostasis during the procedure, an appropriate anesthetic technique with assessment of blood loss in the surgical field, and close monitoring of loss through drainage tubes and hemoglobin levels in the first few hours after the operation. They conclude by establishing that, depending on comorbidity, a range of hemoglobin concentrations between 8.5 g/dL and 10 g/dL can be considered safe during the resection procedure.

In conclusion, we found no difference in survival among patients requiring transfusion of blood products in this series of patients with stage I NSCLC, and so transfusion does not appear to be associated with worse prognosis. We did find that the frequency of transfusions depended on tumor size, histologic type, and whether a pneumonectomy was performed. However, the approach to replacement of lost blood needs to be revised and transfusion of blood products should follow a protocol based on stricter clinical and analytical criteria to avoid unnecessary transfusions so that patients are less exposed to the short and long-term risks associated with use of blood products.

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