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ORIGINAL ARTICLE

Invasive mechanical ventilation in cancer patients. Prior non invasive ventilation is a poor prognostic factor

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Summary

Purpose: *Prior non invasive ventilation (NIV) is associated with an increased mortality in patients with haematological malignancies and acute respiratory failure treated by invasive mechanical ventilation (IMV). We have assessed whether NIV failure is an independent prognostic factor for hospital discharge in a general cancer population treated by IMV.*

Methods: *106 patients with solid tumors and 58 patients with haematological malignancies were eligible for this retrospective study; 41 were treated by NIV before IMV.*

Results: *The main indications for mechanical ventilation were sepsis/shock (35%), acute respiratory failure (33%), cardiopulmonary resuscitation (16%) and neurologic disease (10%). Respectively, 35%, 28% and 24% of the patients were extubated, discharged from the intensive care unit (ICU) and from the hospital. For patients treated with NIV prior to IMV, the rates were 22%, 17% and 10%, respectively. In multivariate analysis, 3 variables were independently associated with a decreased probability of being discharged from the hospital: NIV use before IMV (odds ratio/OR=0.30, 95% confidence interval/CI: 0.09-0.95; p=0.04); leukopenia (OR=0.21, 95% CI: 0.06-0.77; p=0.02) and serum bilirubin >1.1 mg/dl (OR=0.38, 95% CI: 0.16-0.94; p=0.04).*

Conclusion: *NIV failure before IMV is an independent poor prognostic factor in cancer patients treated by IMV.*

Key words: cancer, haematological malignancies, mechanical ventilation, non invasive ventilation

Introduction

IMV in cancer patients is a life-supporting technique associated with a high mortality rate. The crude mortality risk is around 75% in comparison with 25% for patients requiring intensive care without mechanical ventilation [1,2].

NIV was increasingly used during the last decade for the management of acute respiratory failure. Today it is considered as first-line treatment for severe acute exacerbation of chronic obstructive pulmonary disease, for acute cardiogenic pulmonary oedema and, in the immunocompromised patients, for acute hypoxemic respiratory failure [3]. Its efficacy has been shown in both patients with haematological malignancies [4] and with neutropenia [5]. A case-control study demonstrated a reduced mortality in patients treated by NIV in comparison with IMV [1]. In a previous report, we showed that NIV resulted in shorter ventilation duration and ICU stay in cancer patients with acute respiratory failure and 50% of NIV-treated patients were discharged from the hospital but only 25% of those receiving IMV [6]. In a prospective randomised trial, performed in immunosuppressed patients with pulmonary infiltrates, fever and acute respiratory failure including a majority of neutropenic patients with haematological malignancies, early NIV initiation was associated with a significant reduction in the rate of endotracheal intubation and serious complications and with more hospital discharge [7]. In one of our previous studies, we found that cancer patients receiving IMV after NIV failure had a 93% mortality rate [6]. This is in accordance with other publications [2,8] in which mortality rates after NIV failure ranged from 73 to 92%. In patients with haematological malignancies and acute respiratory distress, failure of NIV occurs in half of the patients and is associated with an increased mortality [8].

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The objective of the present retrospective study was to assess whether prior NIV failure was an independent prognostic factor in invasively ventilated cancer patients.

Methods

All adult patients with underlying neoplastic disease admitted in the ICU of the Institut Jules Bordet, a 7-bed unit of a specific cancer hospital, that required IMV for a medical or a surgical complication from January 2000 until December 2007 were eligible with the exclusion of patients that were mechanically ventilated because of elective surgery. In case of multiple admissions for a given patient, only the first episode of ventilation was taken into account.

The following data were retrospectively retrieved from the medical charts:

- demographic data at ICU admission: age, gender
- disease characteristics: type of cancer, time from cancer diagnosis, prior treatments including bone marrow or stem cell transplantation, cancer phase (diagnostic, curative, controllable but no more curable, pivotal when specific treatment aimed at cure or control has failed or palliative care; patients at palliative stage should not be admitted for critical care according to our ICU policy) [9]
- main reason for ICU admission and for mechanical ventilation
- laboratory data at ICU admission: leukocyte count (leukopenia defined as a leukocyte count < 1,000 cells/mm^3), platelet count (severe thrombocytopenia defined as a platelet count < 50,000/mm^3), haematocrit, C-reactive protein, creatininemia, serum urea, total serum bilirubin, serum glucose, serum albumin level, prothrombin time and arterial blood gases
- severity of illness assessed by the SAPS II score
- critical care management: NIV prior to IMV, use of vasopressive drugs, oliguria (defined as an urinary output of < 500 ml/24 h), presence of positive blood cultures, duration of ventilation and hospitalization
- ICU and hospital discharge status.

Patients with "DNR" ("do not resuscitate") orders were excluded because, by definition in our hospital, they are not eligible for IMV.

In case of no contraindication (shock, lowered consciousness, bowel obstruction or copious tracheal secretions), NIV was the first respiratory support used. Patients who failed NIV underwent tracheal intubation and were mechanically ventilated. Criteria for endotracheal intubation included persistence of respiratory failure or haemodynamic instability but also need to protect the airways to manage copious tracheal secretions or alveolar bleeding and intolerance to mask ventilation. IMV was performed with the Evita 4 or Evita XL ventilators (Dräger, Lübeck, Germany). NIV was provided with a standard facial mask by the BiPAP Vision ventilator (Respironics Inc, Murrysville, USA). Characteristics of NIV were: positive end expiratory pressure (between 3 and 11 cm H_2O), pressure support (between 7 and 24 cm H_2O) and FiO_2 were adjusted to patient tolerance and on arterial blood gases. NIV was used for a minimum of 1 h every 4 h but sometimes continuously if necessary to maintain blood arterial haemoglobin oxygen saturation > 90%. When the patient's condition improved, we progressively weaned NIV by 2 cm H_2O increments over a few hours.

This study was approved by our local Belgian ethical committee. No patient/family inform consent was required according to our legislation but we received the accord of the medical doctor in charge of the patient.

Statistical analysis

Observed distributions were summarized using the median for continuous variables or reported using frequency tabulations for categorical variables. The primary evaluation criterion was vital status (alive or dead) at hospital discharge. Logistic regression analysis (logit model for binary dependent variables) was used to assess the relationship between multiple characteristics and the probability of in-hospital mortality. OR together with 95% CI were reported. For multivariate analysis (forward stepwise method for covariates selection), variables with more than 10% missing values were excluded. Variables with rates of missing values less than 10% were tested for inclusion in a multivariate model if they were associated to the outcome with a $p < 0.15$ in univariate analysis (logit model with one independent variable). Variables without missing data were tested if $p < 0.30$ in univariate analysis.

Results

One hundred and ninety-five consecutive patients, of whom 164 were eligible for the present study, required mechanical ventilation during the study period. Thirty-one were excluded for the following reasons: elective surgery (n=21), IMV started in another hospital prior to transfer in our ICU (n=6), non neoplastic disease (n=3) and transfer to another hospital without follow-up (n=1). The eligible patients' characteristics are shown in Table 1. Sixty-five % of the patients had solid tumors and 35% haematological malignancies. Twen-

Table 1. Patient characteristics on admission

Characteristics	*Whole group*	*NIV followed by IMV*	*IMV alone*	*p-value*
Number of patients	164	41	123	
Median age, years (range)	57 (19-81)	49 (23-78)	59 (20-81)	0.008
Gender				0.86
Male, n	95	23	72	
Female, n	69	18	51	
Median SAPS II score (range)	53 (23-94)	56 (23-83)	47 (30-94)	0.002
Type of malignancy, n (%)				<0.001
Solid tumor	106 (64.6)	16 (39.0)	90 (73.2)	
Haematological malignancy	58 (35.4)	25 (61.0)	33 (26.8)	
Bone marrow /Peripheral blood stem cell transplantation, n (%)	37 (63.8)	19 (76.0)	18 (54.5)	<0.001
Cancer phase* (1,2 vs. 3,4), n (%)				0.006
Phase 1	5 (3.0)	1 (2.4)	4 (3.2)	
Phase 2	60 (36.6)	23 (56.1)	37 (30.1)	
Phase 3	89 (54.3)	17 (41.5)	72 (58.5)	
Phase 4	10 (6.1)	0 (0.0)	10 (8.1)	
Leukopenia at admission, n (%)	40 (24.4)	13 (31.7)	27 (21.9)	0.22
Median PaO_2/FiO_2 ratio (range)	215 (46-590)	183 (52-407)	230 (46-590)	0.02

*Cancer phase: 1= diagnostic, 2= curative, 3= controllable but no longer curable, 4= pivotal. IMV= invasive mechanical ventilation, NIV= non invasive ventilation

ty-four % of the patients were leukopenic at admission. Median SAPS II score was 53. Reasons for admission to the ICU and type of complications leading to mechanical ventilation are reported in Tables 2 and 3. Causes for ICU admission were respiratory failure (35%), sepsis/shock (21%), neurologic disturbances (12%) and abdominal pathology (10%) and types of complications leading to mechanical ventilation were sepsis/shock (34%), respiratory failure (33%), cardiopulmonary resuscitation (15%) and neurologic disturbances (10%).

One hundred and twenty-three patients received immediate IMV and 41 were initially treated by NIV followed by IMV.

Thirty-five percent (n=58), 28% (n=46) and 24% (n=38) of the whole patient population were extubated, discharged from the ICU and from the hospital. The re-

Table 2. Reasons for admission to the intensive care unit

Reasons for admission	*Whole group (n=164) %*	*NIV followed by IMV (n=41) %*	*IMV alone (n=123) %*
Respiratory failure	35.3	63.4	26.0
Sepsis/shock	21.3	14.6	23.5
Neurologic disease	12.1	4.8	14.6
Abdominal pathology	10.3	12.1	9.7
Heart disease	7.9	2.4	9.7
Cardiopulmonary resuscitation	7.3	0.0	9.7
Acute renal failure	4.8	2.4	5.7
Other	0.6	0.0	0.8

Table 3. Complications leading to ventilation

Complications	*Whole group (n=164) %*	*NIV followed by IMV (n=41) %*	*IMV alone (n=123) %*
Sepsis/shock	34.7	34.1	34.9
Respiratory failure	33.5	56.1	24.3
Cardiopulmonary resuscitation	15.8	–	21.0
Neurologic disease	10.3	4.8	12.1
Heart disease	3.6	–	4.8
Other	1.8	–	2.4

spective percent values for patients initially treated by NIV and for those receiving immediate IMV were 21.9, 17.1, 9.8% and 39.8, 31.7, 27.6%. Hospital discharge rate was significantly smaller in case of prior NIV (p=0.02).

One-month and one-year survival rates were 30% (95% CI: 23-37) and 9% (95% CI: 4-14). Median survival time was 8 days for the whole group. It was 8 days for patients treated initially with NIV and 7 days for those receiving immediate IMV (log rank test, p=0.47).

Univariate analyses for variables predicting hospital discharge are displayed in Table 4. Bone marrow transplantation, NIV use before IMV, use of vasopressor, leukopenia, bilirubin serum level >1.1 mg/dl, and high SAPS II score were associated with increased mortality whereas age > 60 years, solid tumor, intubation in the first 24 h of ICU admission, bicarbonate serum level ≥ 22 mg/dl, haematocrit > 26%, and platelet count < 50,000/mm³ were associated with lower mortality. We did not detect interaction between the cause of ventilation and the type of ventilation (p=0.66).

Table 4. Univariate analysis of variables predicting hospital discharge alive

Variables		*OR (95% CI)*	*p-value*
Age	≥ 60 vs. <60 years	2.49 (1.19-5.24)	0.02
Gender	Female vs. male	0.87 (0.42-1.82)	0.71
Tumor type	Solid vs. haematological	3.01 (1.23-7.36)	0.02
Stage of solid tumor	Metastatic vs. non metastatic	0.43 (0.18-1.02)	0.06
Phase	Curative vs. controllable	0.75 (0.35-1.60)	0.45
Bone marrow transplantation	Yes vs. no	0.22 (0.06-0.77)	0.02
Surgery	Yes vs. no	1.40 (0.68-2.91)	0.36
Chemotherapy	Yes vs. no	0.61 (0.25-1.49)	0.28
Radiotherapy	Yes vs. no	1.62 (0.78-3.37)	0.19
NIV before IMV vs. immediate IMV	Yes vs. no	0.27 (0.09-0.81)	0.02
	< 24 h	0.34 (0.10-1.21)	0.10
	> 24 h	0.20 (0.03-1.60)	0.13
Intubation in the first 24 h of ICU admission	Yes vs. no	2.42 (1.12-5.25)	0.02
Use of vasopressor	Yes vs. no	0.43 (0.20-0.92)	0.03
Leukopenia	Yes vs. no	0.17 (0.05-0.59)	0.005
C-reactive protein	> 27 vs. < 27 mg/l	1.15 (0.55-2.39)	0.71
Temperature	≥ 38 vs. < 38° C	0.95 (0.40-2.26)	0.91
Blood pressure	≥ 90 vs. < 90 mm Hg	0.99 (0.44-2.24)	0.98
Heart rate	≥ 120 vs. < 120/min	0.47 (0.21-1.07)	0.07
PaO_2/FiO_2	> 216 vs. < 216	0.70 (0.30-1.65)	0.42
Serum bicarbonate	≥ 22 vs. < 22 mEq/l	2.50 (1.14-5.48)	0.02
pH	Normal (7.35-7.45) vs. abnormal	0.76 (0.25-2.32)	0.63
Creatininemia	≥ 1.2 vs. < 1.2 mg/dl	0.61 (0.29-1.28)	0.19
Haematocrit	≥ 26 vs. < 26%	3.05 (1.39-6.69)	0.006
Oliguria	≥ 500 vs. < 500 ml/24 h	5.80 (0.72-46.45)	0.10
Partial thromboplastin time	≥ 63 vs. < 63%	1.90 (0.90-4.04)	0.10
Serum urea	≥ 70 vs. < 70 mg/dl	1.09 (0.53-2.27)	0.81
Serum bilirubin	≥ 1.1 vs. <1.1 mg/dl	0.30 (0.13-0.66)	0.003
Platelet count	≥ 50 000 vs. < 50 000/mm³	3.69 (1.51-9.03)	0.004
Bacteremia	Yes vs. no	0.66 (0.29-1.50)	0.32
Serum albumin level	≥ 2.7 vs. < 2.7 g/dl	2.11 (0.86-5.16)	0.10
Serum glucose	≥ 161 vs. < 161 mg/dl	0.72 (0.34-1.50)	0.37
SAPS II score	≥ 57 vs. < 57	0.38 (0.15-0.98)	0.05
Complication leading to mechanical ventilation	Respiratory failure	1	
	Sepsis/shock	0.86 (0.4-2.15)	0.74
	Cardiopulmonary resuscitation	0.65 (0.19-2.26)	0.50
	Other	2.63 (0.96-7.20)	0.06

For abbreviations see text

Table 5. Multivariate analysis of variables predicting hospital discharge

Variable		*OR (95% CI)*	*p-value*
NIV before IMV vs. immediate IMV	Yes vs. no	0.30 (0.09-0.95)	0.04
Leukopenia	Yes vs. no	0.21 (0.06-0.77)	0.02
Serum bilirubin	≥ 1.1 vs. <1.1 mg/dl	0.38 (0.16-0.94)	0.04

For abbreviations see text

In multivariate analysis (Table 5), 3 variables were independently associated with in-hospital mortality: NIV use before IMV (OR=0.30, 95% CI: 0.09-0.95, p=0.04); leukopenia (OR=0.21, 95% CI: 0.06-0.77, p=0.02) and serum bilirubin >1.1 mg/dl (OR=0.38, 95% CI: 0.16-0.94, p=0.04).

Discussion

In this retrospective study we observed that in a general population of cancer patients including mainly solid tumours, the use of NIV before IMV is an independent predictor of poor prognosis associated with a significantly higher mortality rate. Only 10% of the patients who failed NIV were discharged alive from the hospital.

These results confirm the observation of Azoulay et al. that IMV after NIV failure is an independent factor associated with mortality [10] in a population with a very high (97.3%) predominance of haematological malignancies. However, our series contained 65% solid tumors and 35% haematological malignancies. Adda et al. had also found that failure of NIV in haematological patients was associated with a high (79%) hospital mortality. They found that respiratory rate under NIV, longer delay between admission and NIV first use, need for vasopressors or renal replacement therapy and acute respiratory distress syndrome (ARDS) were associated with NIV failure [8].

The high mortality rate after NIV failure in a population composed mainly of solid tumors can be explained by several reasons. It may reflect a delay in optimal management of these patients because IMV application is delayed by a too long length of time in patients not responding to NIV. Indeed, findings report that inability to increase the PaO_2/FiO_2 ratio after one hour of NIV in ARDS patients predict failure of NIV [11]. However, due to the retrospective nature of the study, we were not able to provide PaO_2/FiO_2 ratio after 1 hour of NIV for all our patients. Such predictors of NIV failure could be used to guide decision for intubation.

We observed that leukopenia in patients requiring mechanical ventilation predicted poor prognosis, confirming the results of our previous study on a series of 168 consecutive cancer patients requiring IMV [12]. Other studies assessing only haematological patients did not observe that leukopenia is a poor prognostic factor probably because the majority of haematological patients are leukopenic. As leukopenia appears of particular importance in our general cancer population, there are some ways to be considered in the management of leukopenic cancer patients requiring mechanical ventilation in order to improve their prognosis. Reducing the duration and the severity of leukopenia, by administering granulocyte colony-stimulating factors, could maybe translate into better prognosis. The safety of this procedure has been tested in intubated ICU patients, with no excess risk for development of ARDS or multiple organ failure [13]. Probably, the best way to improve the prognosis of leukopenic cancer patients is to avoid intubation by performing early NIV.

We found that elevated bilirubin levels were associated with higher in-hospital mortality. Other authors reached to the same conclusions. Simultaneous hepatic (bilirubin >4 mg/dl) and renal dysfunctions (serum creatinine >2 mg/dl) were associated with higher probability of death among patients requiring mechanical ventilation after hematopoietic stem cell transplantation [14]. Bilirubin was a significant predictor of post-discharge survival in bone marrow transplant recipients admitted in the ICU [15]. In another series [16], no patients who required mechanical ventilation for lung injury after bone marrow transplantation survived when either hemodynamic instability or hepatic and renal failure occurred at the same time. The strong correlation between bilirubin and survival may be explained by the fact that elevated bilirubin values are found in patients with severe multiple organ failure.

Study limitations are partly due to the difference in the demographics of the study groups: the NIV group included younger patients, more severely ill and with more severe hypoxemia.

The mortality rate is independent from cancer characteristics. Our group has already demonstrated that the characteristics related to the cancer were not prognostic factors for hospital and in-ICU mortality, while they were factors predicting survival after discharge [17].

Even if NIV failure has bad prognostic value it is important to state that NIV is a very important tool to avoid complications in this patient population and these results do not imply that we change our attitudes towards using NIV.

Conclusion

In a series of cancer patients requiring mechanical ventilation, we observed that NIV failure before IMV is an independent poor prognostic factor in cancer patients treated by IMV. In addition, the patient's prognosis is independent from cancer characteristics.

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