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ORIGINAL ARTICLE

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Non-invasive ventilation for cancer patients with life-support techniques limitation

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Abstract *Goals of work:* The study was conducted to determine the usefulness and efficacy of non-invasive ventilation (NIV) in cancer patients with "life-support techniques limitation" admitted for an acute respiratory distress, in terms of intensive care unit (ICU) and hospital discharges. *Patients and methods:* A total of 18 consecutive cancer patients (17 with solid tumours and one with haematological malignancy) with "life-support techniques limitation" in acute respiratory failure and who benefited from NIV were included. NIV was provided with a standard face mask by the BiPAP Vision ventilator (Respironics Inc.). Variables related to the demographic parameters, SAPS II score, cancer characteristics, intensive care data and hospital discharge were recorded. *Main results:* Complications leading to NIV were hypoxemic respiratory failure in 11 patients and hypercapnic respiratory failure in seven. Total median duration of NIV was 29 h. NIV was applied during a median of 2.5 days with a median of 16 h per day. Total median ICU stay was 7 days (range 1–21). Fourteen and ten patients were discharged from ICU and from hospital, respectively. *Conclusion:* NIV appears to be an effective ventilation support for cancer patients with "life-support techniques limitation".

Keywords Neoplasm · Non-invasive ventilation · Respiratory failure · Life support techniques limitation · Cancer

Introduction

In recent years, non-invasive ventilation (NIV) has been increasingly used in intensive care unit (ICU). Its effectiveness was demonstrated in patients with acute exacerbations of chronic obstructive pulmonary disease [1] and in patients with acute respiratory failure [2].

In a previous study [3], we found that 57.5 and 42.5% of the cancer patients who benefited from NIV were discharged from ICU and from hospital, respectively. The role of NIV in patients for whom there are "life-support techniques limitation" is unclear. However, it appears to be an attractive option to support such cancer patients in respiratory failure for different reasons. It lessens dyspnea and preserves the patient's autonomy, verbal communication and eating. Guidelines for NIV include the possibility to perform such ventilatory support in patient who are "not to be intubated" [4, 5]. Only a few studies evaluated the role of NIV in patients who refused intubation [6–10]. These reports showed favourable short-term outcome.

The aim of our study was to evaluate the usefulness and efficacy of NIV in a group of cancer patients with life-support technique limitations in respiratory failure. We also tried to determine patients' characteristics predicting response to NIV.

Patients and methods

Since January 2000, all consecutive cancer patients requiring non-invasive mechanical ventilation in the ICU of the Institut Jules Bordet, an adult cancer hospital, were

included in our database. For the present study, we considered all eligible patients treated by NIV until April 2004. Patients without underlying neoplastic disease were not eligible. Every patient with a pathologically proven malignant neoplasm, whether the disease was active or in remission, was considered a cancer patient. It should be noted that in our hospital, patients might be attributed a special directive preventing admission to the ICU or application of some invasive life-support techniques according to the cancer status or associated comorbidities. The staff consisting of physicians, including intensivists, decides this directive during regular meetings in the department. In some cases, a decision can be made to refrain from performing some life-supportive critical care techniques like invasive mechanical ventilation, haemodialysis or cardiopulmonary resuscitation, although the patient can still be admitted to the ICU. These patients are called patients with "life-support techniques limitations". For the present study, we only consider the patients of the database who had this "life-support techniques limitation" status.

Patients were eligible when they had respiratory distress defined as: severe dyspnea at rest, profound hypoxia in room air or during nasal oxygen therapy and/or severe hypercapnia, acute cardiogenic oedema non-responding speedily to diuretics and oxygen, clinical decision that the patient required support with mechanical ventilation.

Patients were prospectively recorded and data were retrospectively collected. The following information was retrieved from the medical chart of each patient:

(1) Demographic and clinical data at ICU admission: age, gender, comorbidities (chronic obstructive pulmonary disease, heart disease, steroids therapy).
(2) Characteristics of the neoplastic disease: type of cancer, time since first diagnosis, extent of the tumour (locoregional or disseminated), cancer phase, prior treatment including bone marrow transplantation, time since last treatment, neutropenia at ICU admission (defined as a neutrophil count <1,000/mm^3) and end-of-life decisions ("life-support techniques limitations"). Cancer phase was defined [11] as follows: phase 1 (or diagnosis), when the patient's disease is assessed and appropriate treatment goal and treatment are negotiated; phase 2 (or potential cure), when the goal of the treatment is cure with the risks of associated morbidity; phase 3, when disease is controllable but not curable, when a temporary remission that will significantly prolong life or improve patient's condition may be achievable; phase 4 (or pivotal phase), when specific treatment aimed at cure or control has failed (this is the most critical point in the disease for many cancer patients); and phase 5 (or palliative management).
(3) Cause of ICU admission and reason for non-invasive ventilation.
(4) SAPS II scores, calculated on the basis of the most disturbed value recorded during the first 24 h of stay after ICU admission according to Le Gall et al.[12].
(5) Arterial blood samples just before beginning NIV.
(6) ICU and hospital discharges status (alive, dead) and duration.

The ventilation mode was provided with a standard facial mask by the BiPAP Vision ventilator (Respironics Inc., Murrysville, USA). Positive end expiratory pressure (between 4 and 8 cm H_2O), pressure support (between 10 and 18 cm H_2O) and FiO_2 were adjusted to patient tolerance and to arterial blood gas values. NIV was used for a minimum of 1 h every 4 h, but sometimes used continuously when it became necessary to maintain saturation at more than 90%. When the patient's condition improved, we progressively weaned NIV by 2 cm H_2O decrements over a few hours.

Statistics

Comparison of patients' ICU or hospital discharge status according to their characteristics was made by bilateral Fisher's test in case of binary variable or Mann–Whitney test. Survival was calculated from the date of NIV and estimated via the Kaplan–Meier method. All statistical tests were performed using the software Statistica (Statsoft, Tulsa, OK, USA). A p value lower than 0.05 was considered as statistically significant.

Results

Eighty-seven consecutive cancer patients requiring non-invasive ventilation were admitted to the medical ICU of our cancer hospital between January 2000 and April 2004. Out of this cohort, 18 (20.6%) had "life-support techniques limitation" and were eligible for the study (Table 1). There were 12 men and six women with a median age of 68 years (range 29–81). Seventeen patients had solid tumours (three with locoregional disease and 14 with metastatic disease) and one had a haematological malignancy. Twelve patients had lung cancer, two head and neck cancer, two bladder carcinoma, one prostate cancer and one acute myeloblastic leukaemia. One patient was at the diagnostic phase of its cancer, 15 at the control phase and two at the pivotal phase. Median time since cancer diagnosis was 13.5 months (range 0–141). Median duration from the last anti-neoplastic treatment was 12.5 days (range 0–122). Four patients had chronic obstructive pulmonary disease, two patients received steroids therapy and two presented with heart failure. Median SAPS II score was 41.5 (range 15–58). Three patients (16.6%) had neutropenia at ICU admission. Seven patients of that cohort were already enrolled in our

Table 1 Patients characteristics and outcome

	Sex	Age	Cancer	Stage	Cause of ARF	SAPS II	RR	P_aO_2	P_aCO_2	pH	NIV duration	ICU discharge	Hospital discharge
1	Woman	68	Head and neck	Control	Pneumonia	36	35	51	43	7.33	72	No	No
2	Man	62	NSCLC	Control	Pneumonia	42	28	114	56	7.38	6	Yes	Yes
3	Man	65	NSCLC	Control	Pneumonia	58	27	63	26	7.45	33	No	No
4	Woman	64	NSCLC	Control	Pneumonia	27	30	47	32	7.48	39	Yes	Yes
5	Woman	34	NSCLC	Control	Pneumonia	32	37	33	32	7.43	68	Yes	Yes
6	Man	73	NSCLC	Control	Pneumonia	33	28	42	27	7.50	5	Yes	No
7	Man	75	NSCLC	Pivotal	Pulmonary embolism	41	33	45	43	7.47	22	Yes	Yes
8	Man	68	SCLC	Control	Pneumonia	43	25	37	57	7.33	11	Yes	Yes
9	Man	69	SCLC	Diagnostic	Pneumonia	56	36	42	66	7.29	9	No	No
10	Woman	76	Leukemia	Control	Acute pulmonary edema	49	29	81	69	7.16	29	Yes	No
11	Man	80	Prostate	Control	Acute pulmonary edema	46	32	94	66	7.27	13	Yes	No
12	Woman	30	Bladder	Control	Pleural effusion	15	15	55	38	7.47	68	No	No
13	Man	29	NSCLC	Control	Pulmonary embolism	27	40	26	27	7.46	10	Yes	Yes
14	Man	81	Bladder	Control	Pneumonia	40	28	49	29	7.49	49	Yes	No
15	Man	68	NSCLC	Control	Acute pulmonary edema	50	22	50	65	7.21	19	Yes	Yes
16	Woman	77	NSCLC	Control	Pneumonia	23	20	31	61	7.30	30	Yes	Yes
17	Man	60	NSCLC	Control	Pneumonia	47	34	45	25	7.48	70	Yes	Yes
18	Man	46	Head and neck	Pivotal	Pneumonia	45	41	48	40	7.42	138	Yes	Yes

NIV duration is expressed in hours. P_aO_2 and P_aCO_2, value before NIV (mm Hg)
RR Respiratory rate before NIV (breaths/min), *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *ARF* acute respiratory failure

previous study about the feasibility of NIV in cancer patients [3].

The complications leading to non-invasive ventilation were hypoxemic respiratory failure in 11 patients and hypercapnic respiratory failure in seven. The causes of respiratory failure are described in Table 1. Eleven patients had a neoplastic lung involvement explaining in part that the occurrence of an additional event may precipitate respiratory failure. Tolerance to NIV was considered to be good. No gastric distension and no pneumothorax were described, but some patients had skin redness and irritation over the nose. Two cases of cardiac ischemia and one of atrial fibrillation occurred.

Total median duration of NIV was 29 h (range 5–138) during a median of 2.5 days (range 1–8), with a median of 16 h per day (range: 5–24). Total median duration of ICU stay was 7 days (range 1–21).

Four patients were non-responders to NIV: one due to persistent hypoxia, two by exhaustion and one due to septic shock. Fourteen and ten patients were discharged alive from the ICU and from the hospital, respectively. Patients who were discharged from ICU died of cancer progression (n=5), respiratory failure (n=2), cardiac failure (n=2), cerebral haemorrhage (n=1), sudden death (n=1). In three cases, cause of death was unknown. The overall median survival was 50 days after NIV (mean 92 days, range 0–432). The overall 1-year survival was about 10%. Among the ten patients who were discharged alive from the hospital, nine had lung cancer and one had head and neck cancer, eight were at the control phase of the disease, seven had a metastatic disease, and only one was neutropenic. Median survival was 69 days (mean 69 days, range 41–432) after NIV for those patients who were discharged alive from the hospital.

Seventy-five percent of patients with lung cancer who benefited from NIV were discharged alive from hospital, whereas only 16% of patients with other types of tumours who received NIV were discharged (p=0.03). We found no difference between the two groups (survivors and non-survivors) in term of pH, P_aCO_2, P_aO_2, respiratory rate, SAPS II or type of respiratory failure (hypercapnia vs hypoxemia) (Table 2).

Table 2 Baseline characteristics of the patients

	Patients discharged from hospital	Patients dead in hospital
Median pH (range)	7.42 (7.21–7.48)	7.39 (7.16–7.50)
Median P_aCO_2 (range)	41.5 (25–65)	40.5 (26–69)
Median P_aO_2 (range)	45 (26–114)	53 (42–94)
Median RR (range)	29 (20–41)	28.5 (15–36)
Cause of respiratory failure		
Hypercapnia	*N*=4	*N*=3
Hypoxemia	*N*=6	*N*=5
Median SAPS II (range)	41.5 (23–50)	43 (15–58)

P_aO_2 and P_aCO_2, value before NIV (mm Hg)
RR Respiratory rate before NIV (breaths/min)

Discussion

In our series of 18 cancer patients with "life-support techniques limitation" who received NIV for respiratory failure, 77.7 and 55.5% of the patients were discharged from ICU and from hospital, respectively. Seventy-five percent of patients with lung cancer who benefited from NIV were discharged alive from the hospital. We found no other initial patient characteristic predictive of NIV success. Median survival time after NIV start was 50 days and the overall 1-year survival was 10%.

The role of NIV in patients who are "not to be intubated" has been described in a few reports. Meduri et al. [7] reported the cases of 11 terminally ill patients (but only three with cancer) who refused endotracheal intubation. They benefited from NIV with a facial mask either for hypercapnic (nine patients) or for hypoxemic (two patients) acute respiratory failure. NIV was effective in seven out of the 11 patients, all of whom survived and were discharged from the ICU, whereas five patients were discharged from hospital. The four patients who died were hypercapnic. In another study [13], Meduri et al. reported the cases of 26 patients (three with lung cancer) with advance-stage diseases [end-stage chronic obstructive pulmonary disease (COPD), liver disease, AIDS] who refused intubation. Nine patients died during their ICU stay. In five of these patients, NIV was discontinued at the patient's or family's request after failure to improve. In a third study, nasal ventilation was selected as the last therapeutic resort in 17 elderly non-cancer patients for which endotracheal intubation was contra-indicated [8]. NIV was successful in ten of 17 patients but nine patients died in hospital. A recent study evaluated the role of NIV in 37 chronic obstructive pulmonary disease patients who had the do-not-intubate code and who developed acute respiratory failure [6]. Median survival was 179 days with a 1-year survival of about 30%. The majority of survivors developed another life-threatening event in the following year. Levy et al. [9] reported a series of 114 patients with do-not-intubate orders treated with NIV. In this population, which includes 14 patients with malignancies, 43% patients survived hospital discharge. Finally, Cuomo et al. [10] investigated the role of NIV in 23 patients with solid malignancies receiving palliative care and who were in acute respiratory failure. Thirteen of these patients were successfully ventilated with NIV and discharged alive. Two patients failed NIV and accepted invasive ventilation and eight died after initial NIV. In this study, a higher SAPS II and a lower P_aO_2/FiO_2 were associated with a lower survival and the 1 year mortality rate was 87%.

To the best of our knowledge, this is the first study evaluating the role of NIV in a general population of cancer patients with acute respiratory failure and who have all "life-support techniques limitation" but who are not in palliative care units. The success rate of 77.7 and 55.5% for ICU and hospital discharge, respectively, that we obtained in the context of severely ill cancer patients is encouraging. This point can be explained by the fact that it has been demonstrated that the prognosis of cancer patients admitted to ICU for a medical problem is first determined by the acute physiologic changes induced by the complication, as evaluated by the severity scores and not by the cancer itself [14]. In another study, we have also shown that gravity scores were the single independent predictors for hospital mortality in 247 cancer patients admitted for a medical acute complication in an intensive care unit [15]. However, only 10% of the patients survived after 1 year. This poor survival rate can be explained by the fact that, after recovery from complications, characteristics relating to the neoplastic disease retrieve their independent influence on further survival [14]. Indeed, 90% of the patients discharged from the hospital were lung cancer patients who presented poor prognosis. One-year survival in this population is around 10%. No significant predictive factor of NIV success has been demonstrated in our study: neither the cause of respiratory failure, nor the initial blood gases, nor the respiratory rate nor the SAPS score. Nevertheless, the number of patients in our study is small, which precludes any meaningful conclusion on this point.

The cases included in our study are patients in respiratory distress who need ventilatory support. A few years earlier, these patients would have required intubation and mechanical ventilation. Today, with the arrival of NIV, this technique is often offered (when not contra-indicated) as first ventilatory support and, if ineffective, patients are then intubated. However, if life-support technique limitations have been decided because the tumor has reached a far-advanced stage, in our policy, these patients are not eligible for invasive techniques and NIV is thus the last possible option of ventilatory support. This situation happens quite frequently in our Institution, especially in cases of lung tumours. Lung cancer patients are often COPD patients. Moreover, with chemotherapy, infections (e.g. pneumonia

and bronchitis) are common. COPD, involvement of lung by cancer and lung infections are thus frequent and can lead to respiratory distress.

NIV is generally well tolerated and can prolong life, allowing other anti-cancer therapy or eventually life closure tasks to be completed. Indeed, NIV lessens dyspnea and permits eating, drinking and communication. However, we have to be very careful and refrain from prolonging survival in a futile manner in patients whose death is inevitable. NIV should thus be proposed in cancer patients who still have a therapeutic plan and who present a reversible cause of acute respiratory failure. In our institution, patients with too advanced cancer might be attributed a special directive preventing either admission to the ICU or the application of some invasive life-support techniques. The staff of physicians, including intensivists and oncologists, may decide in some of these cases not to perform some life-supportive critical care techniques such as invasive mechanical ventilation, hemodialysis or cardiopulmonary resuscitation. In the second option, the patient can be admitted in the ICU, e.g. for NIV.

We conclude that NIV is an effective and comfortable method of supporting cancer patients with "life-support techniques limitations" who still have a therapeutic plan and a reversible cause of acute respiratory failure.

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