Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013; 14: 338–345

informa
healthcare

EPIDEMIOLOGY

The impact of clinical factors, riluzole and therapeutic interventions on ALS survival: A population based study in Modena, Italy

ELENI GEORGOULOPOULOU[1], NICOLA FINI[1], MARCO VINCETI[2], MARCO MONELLI[3], PAOLO VACONDIO[4], GIORGIA BIANCONI[5], PATRIZIA SOLA[1], PAOLO NICHELLI[1] & JESSICA MANDRIOLI[1]

[1]*Department of Neuroscience, S. Agostino-Estense Hospital and University of Modena and Reggio Emilia,* [2]*Department of Clinical and Diagnostic Medicine and of Public Health, University of Modena and Reggio Emilia,* [3]*Section of Respiratory Diseases, Department of Oncology, Haematology, and Respiratory Diseases, Modena University Hospital,* [4]*Department of Primary Care, Health District and* [5]*Administration Department, Psychosocial Sector, Modena University Hospital, Modena, Italy*

Abstract

The prognostic role of riluzole, enteral nutrition (EN), non-invasive ventilation (NIV) and interdisciplinary care in ALS is still debated. A population based study has been performed focusing on ALS survival, with particular attention to prognostic factors and therapeutic intervention. All patients diagnosed with ALS between 2000 and 2009 and residing in Modena, Italy, have been registered. A centre for motor neuron disease (MND) has been active in our province since 2000, in addition to a prospective registry collecting all incident cases. One hundred and ninety-three incident cases have been collected during the 10 years of the study. Results demonstrated that median survival was 41 months (the overall three-year and five-year survival rates being 54.36% and 28.81%, respectively). Based on univariate analysis, factors related to survival were: age at diagnosis, gender, site of onset, phenotype, riluzole treatment and tracheostomy. In the Cox multivariable model, the factors independently related to a longer survival were age ($p < 0.01$), site of onset ($p = 0.02$) and riluzole treatment ($p < 0.01$), with a median gain in survival of 29 months (patients aged < 55 years compared with patients ≥ 55 years), 20 months (spinal versus bulbar onset), and 12 months (riluzole, yes vs. no), respectively. In conclusion, the study has confirmed the prognostic role of clinical features, but has surprisingly demonstrated that riluzole prolonged life significantly longer than NIV and EN. This observational study described the effects of ALS management in a setting that may approximate routine clinical practice more closely than randomized controlled trial (RCT); effects of uncontrolled potential confounders, however, cannot be excluded.

Key words: *Survival, prognostic factors, therapeutic intervention, riluzole*

Introduction

Although the mean survival of ALS patients from symptom onset is often reported to be three to five years, published studies report a wide range of outcomes, which narrows when considering population based studies (1).

A number of clinical factors predict ALS prognosis: age and site of onset, the severity and rate of disease progression, degree of diagnostic certainty, diagnostic delay, and cognitive impairment (2).

The role of therapeutic interventions (riluzole, enteral nutrition (EN), non-invasive ventilation (NIV) and interdisciplinary care) is still debated; nevertheless, some studies have documented that they are accompanied by a higher survival rate (3–7).

A population based study focusing on ALS survival, with particular attention to possible clinical prognostic factors and therapeutic intervention, was performed. Our aim was to study demographic and clinical factors influencing ALS survival as well as the role of pharmacological treatment and of nutritional and ventilatory management on ALS prognosis.

Correspondence: J. Mandrioli, S. Agostino-Estense Hospital and University of Modena and Reggio Emilia, Via Pietro Giardini n. 1355, 41100 Modena, Italy. Fax: 00 39 0593962409, 00 39 0593961701. E-mail: j.mandrioli@ausl.mo.it

(Received 19 August 2012; accepted 30 December 2013)

ISSN 2167-8421 print/ISSN 2167-9223 online © 2013 Informa Healthcare
DOI: 10.3109/21678421.2013.763281

Materials and methods

Patient data collection

The study was performed in the province of Modena (population 694,580) focusing on patients diagnosed with ALS from 2000 to 2009. A centre for motor neuron disease (MND) has been active in our province since 2000, in addition to a prospective registry collecting all incident cases. At the MND centre, where clinical and therapeutic information was collected at each visit, patients underwent a regular multidisciplinary follow-up at least every 3–4 months (8).

When patients were no longer able to reach the centre, they were monitored at their home or in a nursing home by the Integrated Home Care of the Italian National Health System, together with pulmonologists and neurologists from the centre.

Patients with possible, probable, and definite ALS, and who resided in Modena, have been noted or sent to our centre from the neurological departments of the province, from general practitioners, from local neurophysiology units, and from outpatient consultants (199 patients).

This source was implemented by cases resulting from the provincial hospitals as having a discharge code of 335.2 of the International Classification of Diseases (ICD, 9th rev.) (two patients), and by death certificates among residents from 2000 to 2009 reporting the above mentioned code (12 patients).

In these cases we collected information from the general practictioner.

Overall, during the 10 years of study, 213 residents in the province of Modena were diagnosed with ALS. Only definite or probable diagnosis of ALS was considered for the study, leading to a total of 193 incident cases during the period of observation. In the remaining 20 cases, initially a possible ALS was diagnosed, but the follow-up pointed towards other diagnoses (8).

Of the 193 patients, a total of 179 cases had complete recordings of symptoms at onset, symptoms and signs at diagnosis, and phenotype. For the 14 cases resulting from hospital discharge and death certificates, the available data included demographic data, riluzole treatment, time of onset, diagnosis and death.

Statistical methods

Descriptive statistics were performed using Student's *t*-test and χ^2 test where appropriate.

Survival was calculated from onset to death/tracheostomy or censoring date (last day of follow-up, 31 December 2011) using the Kaplan-Meier method. The curves were compared with the log-rank test. Multivariable analysis was performed with Cox's proportional hazards model.

A p-value < 0.05 was considered significant.

All calculations were performed with the STATA statistical package, V.10 (2007).

Results

During the 10 years of study, 193 incident cases were collected. Clinical features and demographic data have been reported in detail elsewhere (8).

Two separate analyses of survival were performed: one for time from onset to death, the other for time from onset to death or tracheostomy (tracheostomy-free survival).

The median survival time from onset to death was 41 months (SE 2.28, CI 35–46). The overall one-year, two-years, three-years, four-years and five-years survival rates were 93.78% (SE 1.74%), 75.13% (SE 3.11%), 54.36% (SE 3.59%), 36.11% (SE 3.55%), and 28.81% (SE 3.41%), respectively

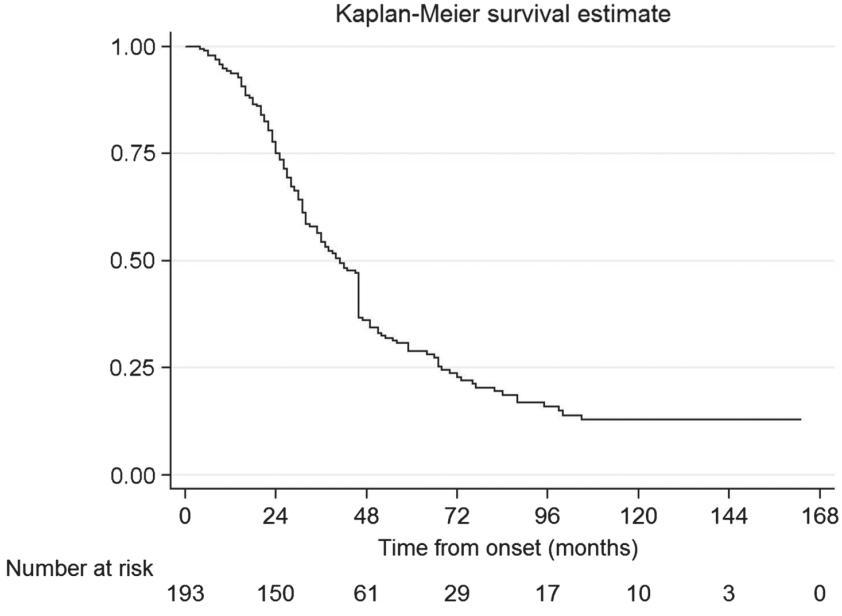

Figure 1. Overall Kaplan-Meier survival estimates (survival from onset to death).

Table I. Survival from onset to death, and tracheostomy-free survival.

Variable	Type	Survival (months to death), median (95% CI)	p^*	Survival (months to death or tracheostomy), median (95% CI)	p^*
Gender	Male	46 (40–59)	<0.01	45 (37–49)	<0.01
	Female	32 (28–41)		31 (27–36)	
Onset	Spinal	46 (37–59)	<0.01	38 (35–46)	<0.01
	Bulbar	26 (22–30)		26 (22–30)	
Age at diagnosis	<55 yrs	68 (46 to -)	<0.01	47 (38–68)	<0.01
	55–74 yrs	37 (32–49)		36 (31–43)	
	>74 yrs	30 (24–41)		30 (24–41)	
Phenotypes	Bulbar	26 (23–42)	<0.01	26 (23–38)	<0.01
	Classic	32 (28–40)		31 (28–38)	
	Flail	67 (37–76)		62 (37–70)	
	UMNp	67 (36 to -)		42 (29–66)	
	Respiratory	18 (4 to -)		18 (4 to -)	
FTD	Yes	31 (23–49)	0.62	31 (23–49)	0.73
	No	42 (35–46)		37 (32–45)	
Riluzole	Yes	43 (37–51)	<0.01	38 (35–43)	0.11
	No	31 (25–46)		31 (25–46)	
ALS centre	Yes	40 (33–46)	0.57	36 (31–41)	0.69
	No	46 (31–46)		42 (31–46)	
EN	Yes	41 (32–46)	0.66	36 (30–40)	0.02
	No	43 (32–46)		43 (32–46)	
NIV	Yes	42 (36–53)	0.23	38 (32–42)	0.38
	No	36 (31–46)		36 (30–46)	
IV	Yes	67 (41–73)	<0.01	NA	NA
	No	36 (31–46)		NA	
Year of diagnosis	2000–05	42 (32–47)	0.91	40 (31–46)	0.04
	2006–09	41 (32–46)		36 (28–41)	

NA: not applicable; "-": lack of observations.
*p-value obtained using log-rank test.

(Figure 1). At 10 years of follow-up, 12.83% of patients were still alive.

With regard to time from onset to death or tracheostomy, the median survival was 37 months (SE 2.27, CI 32–42). The overall one-year, two-years, three-years, four-years and five-years survival rates were 93.78% (SE 1.74%), 73.58% (SE 3.17%), 50.73% (SE 3.60%), 30.59% (SE 3.40%), and 23.09% (SE 3.14%), respectively. After 10 years of follow-up, 6.22% of patients were still alive and tracheostomy free.

Table I shows median survival from onset to death, and median tracheostomy-free survival

According to the univariate analysis, factors related to survival from onset to death were: age at

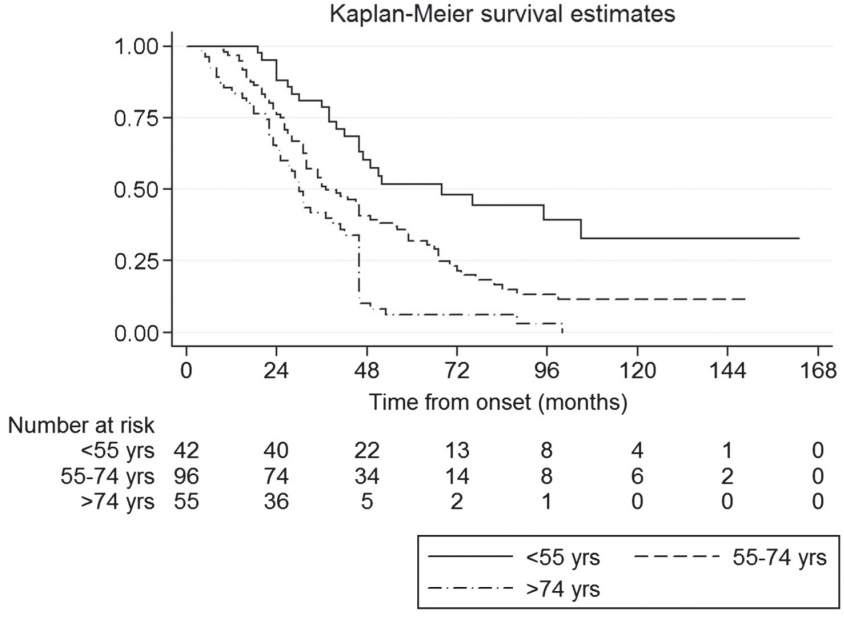

Figure 2. Kaplan-Meier survival estimates according to age at diagnosis (survival from onset to death)

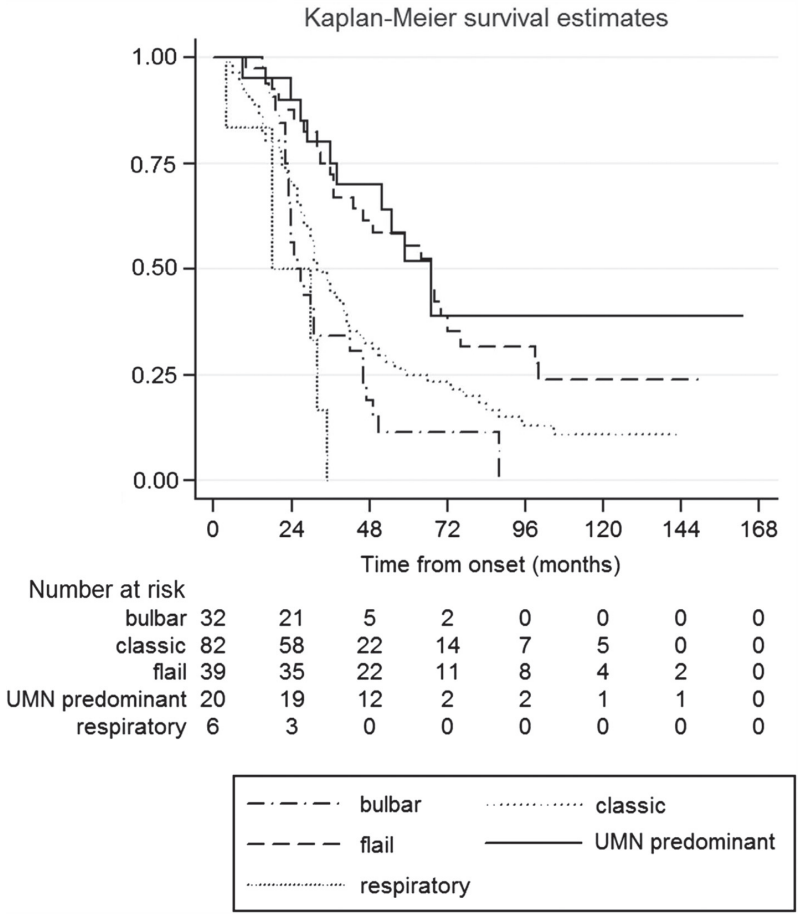

Figure 3. Kaplan-Meier survival estimates according to clinical phenotype (survival from onset to death).

diagnosis (Figure 2), gender, site of onset, phenotype (Figure 3), riluzole treatment (Figure 4), and tracheostomy (Figure 5) (Table I).

In the initial Cox multivariable model, we included the following variables: gender, age at diagnosis, site of onset, phenotypes, presence/absence of

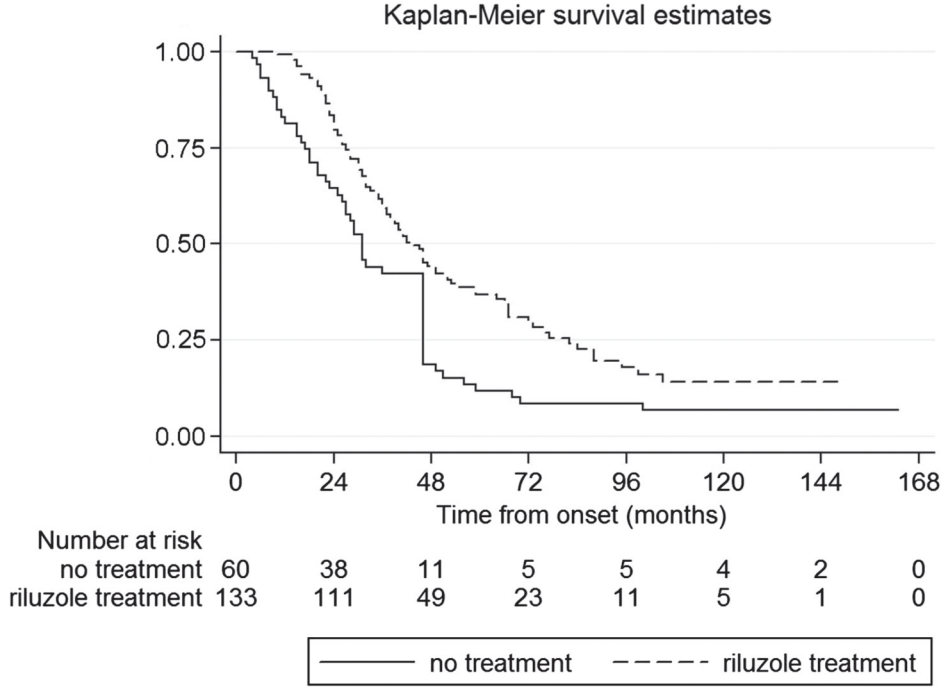

Figure 4. Kaplan-Meier survival estimates according to riluzole treatment (survival from onset to death).

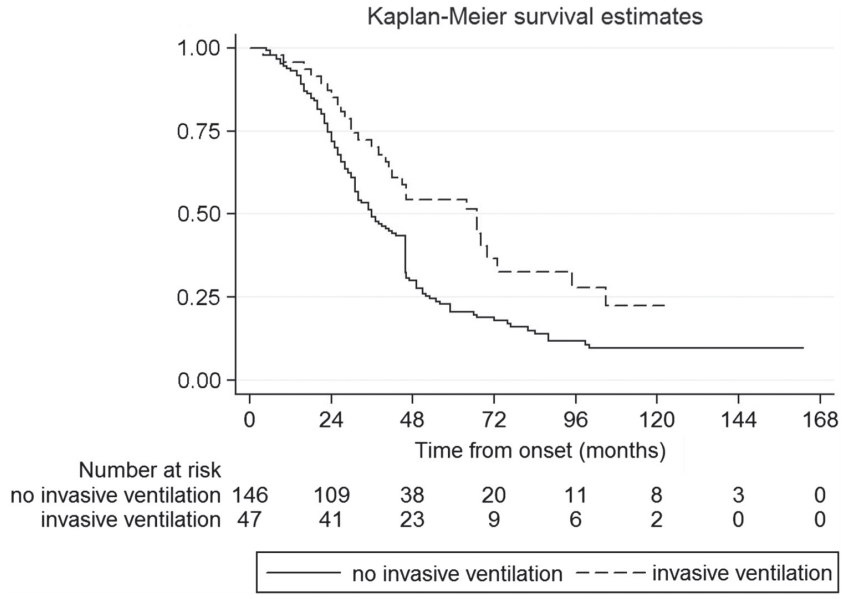

Figure 5. Kaplan-Meier survival estimates according to invasive ventilation (survival from onset to death).

FTD, familiarity, riluzole treatment, multidisciplinary follow-up, EN, NIV, invasive ventilation through tracheostomy (IV), year of diagnosis.

From the initial model, factors independently related to a longer survival were age at diagnosis ($p < 0.01$), site of onset ($p = 0.02$), and riluzole treatment ($p < 0.01$).

After dropping non-significant terms, the final model included age at diagnosis, riluzole treatment, and site of onset (all with a level of significance $p < 0.01$).

At univariate analysis, factors related to tracheostomy-free survival were age at diagnosis, gender, site of onset, phenotype, and year of diagnosis (Table I).

In the Cox multivariable model, we included the following variables: gender, age at diagnosis, site of onset, phenotypes, presence/absence of FTD, familiarity, riluzole treatment, multidisciplinary follow-up, EN, NIV, year of diagnosis. From the initial model, factors independently related to a longer survival were age at diagnosis ($p < 0.01$), site of onset ($p = 0.03$), year of diagnosis ($p = 0.03$), and riluzole treatment ($p < 0.01$).

After eliminating non-significant terms, the final model included age at diagnosis ($p < 0.01$), riluzole

Table II. Stratified analysis of survival (tracheostomy-free survival).

	Variables (factors possibly related to survival)				
Subgroups	Age at diagnosis: <55, 55–74, >74 yrs, Mths* (*p*-value)**	Onset (B/S), Mths* (*p*-value)**	Riluzole treatment (yes/no), Mths* (*p*-value)**	EN (yes/no), Mths* (*p*-value)**	Year of diagnosis (before 2006/from 2006 onwards), Mths* (*p*-value)**
Age at dg < 55 yrs	NA	42/52 (0.11)	46/68 (0.12)	46/− (0.02)	49/40 (0.17)
Age at dg 55–74 yrs	NA	26/37 (0.01)	36/27 (0.48)	35/37 (0.03)	35/36 (0.30)
Age at dg > 74 yrs	NA	24/31 (0.11)	30/29 (0.68)	29/31 (0.22)	31/25 (0.32)
Bulbar onset	42/26/24 (0.11)	NA	30/17 (<0.01)	30/16 (<0.01)	29/25 (0.84)
Spinal onset	52/37/31 (<0.01)	NA	40/29 (0.47)	37/49 (<0.01)	46/36 (0.04)
Classic phenotype	46/32/28 (<0.01)	21/36 (<0.01)	36/27 (0.13)	36/31 (0.85)	31/31 (0.12)
Bulbar phenotype	46/24/25 (0.37)	27/23 (0.12)	28/23 (0.08)	28/17 (<0.01)	31/24 (0.34)
Flail phenotype	76/59/33 (0.20)	−/64 (0.54)	62/32 (0.43)	46/72 (0.04)	68/49 (0.35)
UMNp phenotype	38/59/9 (<0.01)	29/42 (0.74)	52/29 (0.71)	38/112 (0.03)	52/42 (0.91)
Respiratory phenotype	−/32/18 (0.13)	18/32 (0.29)	30/4 (0.06)	18/− (0.13)	−/18 (0.12)
ALS centre	46/36/25 (0.01)	27/38 (<0.01)	38/22 (<0.01)	36/37 (0.01)	43/32 (0.02)
No ALS cntre	95/32/46 (0.04)	17/38 (<0.01)	40/46 (0.84)	31/46 (0.26)	31/46 (0.84)
Diagnosis before 2006	49/35/31 (<0.01)	29/46 (<0.01)	46/31 (0.16)	46/31 (0.24)	NA
Diagnosis from 2006	40/36/25 (0.04)	25/36 (0.10)	36/26 (0.21)	30/46 (0.03)	NA

NA: not applicable; "-": absence of observations; Mths: months; B/S: bulbar/spinal; EN: enteral nutrition; UMNp: upper motor neuron predominant.
*Median survival in months.
**Log-rank test.

Table III. Chacteristic of patients treated or not with riluzole.

Variable	Patients treated with riluzole ($n = 133$)	Patients who did not take riluzole ($n = 60$)	p-value	Total
Gender				
Male	76	26	NS	102
Female	57	34		91
Site of onset				
Spinal	96	32	NS	128
Bulbar	36	15		51
Phenotype				
Classic	54	28	0.04	82
Bulbar	27	5	NS	32
Flail	30	9	NS	39
UMNp	17	3	NS	20
Respiratory	4	2	NS	6
Attendance at multidisciplinary clinic				
Multidisciplinary clinic	126	16	<0.01	142
Other neurological departments or general practitioner	7	44		51
Familiarity				
Familial ALS	7	4	NS	11
Sporadic ALS	126	56		182
Dementia				
ALS + dementia	14	5	NS	19
Pure ALS	119	55		174
Age at diagnosis				
<55 years	38	4	0.01	42
55–74 years	73	23	0.05	96
>74 years	22	33	<0.01	55
Mean age at onset (years), mean (SD)	62.51 (12.53)	71.39 (10.18)	<0.01	64.64 (12.55)
Mean age at diagnosis (years), mean (SD)	63.65 (12.38)	72.99 (10.21)	<0.01	66.56 (12.49)
Mean time onset− diagnosis (months), mean (SD)	13.69 (11.80)	12.59 (10.46)	NS	13.35 (11.79)
EN				
Yes	81	14	<0.01	95
No	52	46		98
Mean time from diagnosis to enteral nutrition (days), mean (SD)	586.60 (398.70)	354.43 (343.55)	0.04	552.02 (396.93)
NIV				
Yes	80	12	<0.01	92
No	53	48		101
Mean time from diagnosis to NIV (days), mean (SD)	627.80 (548.03)	253.25 (196.93)	<0.01	591.70 (535.46)
IV				
Yes	39	8	0.03	47
No	94	52		146
Mean time from diagnosis to IV (days), mean (SD)	884.05 (729.97)	338.29 (456.08)	0.04	799.16 (719.23)
TOTAL	133	60	NA	193 (100.00)

SD: standard deviation; NS: not statistically significant; NA: not applicable; Mths: months; B/S: bulbar/spinal; EN: enteral nutrition; NIV: non-invasive ventilation; IV: invasive ventilaiton; UMNp: upper motor neuron predominant.

treatment ($p < 0.01$), site of onset ($p = 0.02$), year of diagnosis ($p = 0.01$), and EN ($p = 0.04$)

A stratified analysis of tracheostomy-free survival was also performed focusing on the above mentioned factors among the following subgroups: patients diagnosed before 2006 and patients diagnosed from 1 January 2006 onwards, patients younger than 55 years of age, 55–74 years of age, and older than 74 years of age at diagnosis; patients with bulbar or spinal onset; patients with different phenotypes (bulbar, classic, predominant upper motor neuron (pUMN), flail, respiratory); and patients attending or not the ALS centre (Table II).

Overall, patients treated with riluzole survived significantly longer than patients not treated (Table II), and the characteristics of patients treated with riluzole are reported in Table III.

Using the Cox multivariable model, in younger and middle aged patients we could not identify any factor independently related to a longer survival; in elderly patients riluzole treatment ($p = 0.02$), bulbar onset ($p = 0.03$), and time of diagnosis ($p < 0.01$) were independently related to survival.

In the Cox multivariable model, the factors independently related to a longer survival in bulbar- onset patients were age ($p = 0.05$), riluzole treatment ($p = 0.05$), and EN ($p = 0.05$); in spinal-onset patients factors independently related to a longer survival were age ($p = 0.01$), riluzole treatment ($p = 0.05$), EN ($p < 0.01$), and time of diagnosis ($p = 0.02$)

Discussion

Our study confirms the expected role of some well known prognostic factors on ALS survival: age at diagnosis (with younger patients surviving longest), and site of onset (bulbar onset worse than spinal onset) (9).

The vast majority of studies have found that age and site of onset greatly influence a wide range of clinical features, including progression to the end-stage, and the entire clinical phenotypes of ALS, with decreasing survival time correlating with increasing age (10,11). The underlying mechanism is still unknown, although one may speculate that subpopulations of the motor neurons may be differentially vulnerable to the aging process, and that the smaller motor neuron 'reserve' in elderly patients could contribute to an acceleration of the disease.

In our study riluzole treatment was a strong and independent factor related to survival with a gain in survival from onset to death of 12 months in 50% of patients.

Several studies have found a positive, independent, effect of this drug on the outcome of ALS patients (4). In the first RCT, at 12 months, 42% of the patients given placebo had died or undergone tracheostomy compared with only 26% of patients treated with riluzole. The difference was significant, but the effect was attributed completely to the improved survival rate among the 32 patients with bulbar onset (12). This lead various authors to hypothesize the existence of some bias in that study (13) and lead to other larger RCTs which confirmed a small benefit on survival (two to three months) (4).

Conversely, subsequent studies have suggested that treatment with riluzole may be associated with a median survival prolongation of 10 months to as many as 21 months (14–17). A recent population based study in Italy found the benefit of an overall survival rate of six months, which was significant in bulbar-onset and in elderly patients, but not in limb-onset patients (18).

This discrepancy has been confirmed in our study. Riluzole was found to have an independent effect on survival, and in particular on bulbar-onset patients.

Moreover, in our study the effect of riluzole was independent from NIV or EN use. Patients who were treated with riluzole accepted EN and NIV more frequently than patients who were not. However, the time from diagnosis to EN and NIV treatments was significantly longer in patients taking riluzole. These data indicate that riluzole slows the disease and prolongs the time to the need for respiratory and nutritional support.

Conversely, some factors indicated as prognostic in the literature had no impact on ALS survival in our study; median survival of patients who underwent NIV or EN was not significantly different from survival of patients who did not undergo those procedures.

Current guidelines on ALS management recommend multidisciplinary care better able to target the broad and varied needs of persons with ALS throughout the course of the disease (19). More controversial is the impact of multidisciplinary care on ALS survival (20–22).

In our study, among patients attending the ALS centre, only bulbar-onset patients had a significant gain of survival (10 months for 50% of patients). This can be explained by an advanced use of therapeutic intervention, e.g. EN, in patients attending the centre compared to patients not attending the centre (5).

Finally, as expected, at univariate analysis, IV played a significant role on survival to death, with a gain in survival of 52 months for 25% of patients and of 29 months for 50% of patients. Invasive ventilation was not a prognostic factor in multivariate analysis. This result could be explained again by the prognostic role of age at diagnosis: IV is chosen by younger people, who survive longer (23).

A limit of this study is represented by the relatively small number of patients, especially when divided into groups for stratified analysis of survival.

In addition, the current study has all the limitations of observational studies, which are not the gold standard method to evaluate the effect of a treatment because of the result of the effects of uncontrolled potential confounders on survival, which may create bias as a consequence. Nevertheless, observational studies have the advantage of longer-term follow-up than the RCTs (24,25) and include participants who approximate routine clinical practice more readily than RCTs. Patients enrolled in clinical trials do not satisfactorily represent the ALS population (26), as they are usually younger, have a spinal onset, and have a longer diagnostic delay.

In conclusion, it has been confirmed that age at diagnosis and site of onset have an important role on ALS survival as independent prognostic factors. It has been demonstrated that, in our sample, riluzole prolonged life significantly longer than NIV and EN. Although our study may not have shown an independent role of multidisciplinary care, EN, and NIV on ALS survival, these therapeutic interventions improve quality of life in such a manner that widespread use is strongly advocated.

More studies are needed on factors influencing survival and what kind of patients benefit from a given treatment – in particular, to determine whether older patients, patients treated earlier, or patients with a more advanced and longstanding disease derive the same benefit.

Acknowledgements

The authors thank all the collaborators of the multidisciplinary centre for motor neuron disease in Modena, S. Agostino-Estense Hospital: Alessia Verduri, Alessandro Marchioni, Gaia Cappiello, Michele Giovannini, Rossano Dallari (pulmonologists), Giovanni

Pinelli (Urgent Care Medicine- Intensive Care Medicine), Raffaele Stacca, Andrea Marudi (Intensive Care Medicine- Anaesthesiology), Anna Laura Fantuzzi, Silvia Raggi, Francesca Cortesi (dietitians), Vincenzo Giorgio Mirante (gastroenterologist), Carla Budriesi, Federica Frigieri, Eleonora Rossi (speech pathologist), Elisabetta Genovese, Maria Consolazione Guarnaccia (otolaryngologists), Sarah Scandone (psychologist), Gabriele Greco, Mario Santangelo, Stefano Amidei (neurologists), Stefano Cavazza, Elisa Farina, Luciano Mazzoleni, Valter Gherardi, Gianpaolo Galli, Massimo Albuzza (rehabilitation physicians), The Italian ALS Association (AISLA), section of Modena, the Association 'Amici per la Vita', section of Sassuolo, Modena.

Declaration of interest: The authors alone are responsible for the content and writing of the paper.

This work has been supported by a grant to J. Mandrioli and E. Georgoulopoulou from The Italian ALS Association (AISLA), section of Modena.

References

1. Beghi E, Chiò A, Couratier P, Esteban J, Hardiman O, Logroscino G, et al. The epidemiology and treatment of ALS: focus on the heterogeneity of the disease and critical appraisal of therapeutic trials. Amyotroph Lateral Scler. 2011;12:1–10.
2. Chiò A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, et al. Prognostic factors in ALS: a critical review. Amyotroph Lateral Scler. 2009;10:310–23.
3. Radunovic A, Annane D, Jewitt K, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2009;4:CD004427.
4. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev 2012;3:CD001447.
5. Ng L, Khan F, Mathers S. Multidisciplinary care for adults with amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database Syst Rev 2009;4:CD007425.
6. Katzberg HD, Benatar M. Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2011;1:CD004030.
7. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. Lancet Neurol. 2006;5:140–7.
8. Georgoulopoulou E, Vinceti M, Bonvicini F, Sola P, Goldoni CA, de Girolamo G, et al. Changing incidence and subtypes of ALS in Modena, Italy: a 10-years prospective study. Amyotroph Lateral Scler. 2011;12:451–7.
9. Logroscino G, Traynor BJ, Hardiman O, Chio A, Couratier P, Mitchell JD, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry. 2008;79:6–11.
10. Chiò A, Calvo A, Moglia C, Mazzini L, Mora G; PARALS study group. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry. 2011;82:740–6.
11. Atsuta N, Watanabe H, Ito M, Tanaka F, Tamakoshi A, Nakano I, et al. Age at onset influences on wide-ranged clinical features of sporadic amyotrophic lateral sclerosis. J Neurol Sci. 2008;276:163–9.
12. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med. 1994;330:585–91.
13. Rowland LP. Riluzole for the treatment of amyotrophic lateral sclerosis: too soon to tell? N Engl J Med. 1994; 330:636–7.
14. Mitchell JD, O'Brien MR, Joshi M. Audit of outcomes in motor neuron disease (MND) patients treated with riluzole. Amyotroph Lateral Scler Other Motor Neuron Disord. 2006;7:67–71.
15. Traynor BJ, Alexander M, Corr B, Frost E, Mahon L, Hardiman O. Riluzole and prognosis in ALS: findings of the Irish ALS register over a five-year study period (1995–2000). Amyotroph Lateral Scler Other Motor Neuron Disord. 2001; 2(Suppl 2):43–4.
16. Brooks BR, Belden DS, Roelke K, Parnell J, Peper S, Houdek A, et al. Survival in non-riluzole treated amyotrophic lateral sclerosis (ALS) – motor neuron disease (MND) patients with disease onset before and since 1996 is identical: a clinic-based epidemiological study. Amyotroph Lateral Scler Other Motor Neuron Disord. 2001;2:60–1.
17. Turner MR, Bakker M, Sham P, Shaw CE, Leigh PN, Al-Chalabi A. The Kings' Database 1999–2000: an analysis of the effect on survival of interventions in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2001;2(Suppl 2):43.
18. Zoccolella S, Beghi E, Palagano G, Fraddosio A, Guerra V, Samarelli V, et al. Riluzole and amyotrophic lateral sclerosis survival: a population based study in southern Italy. Eur J Neurol. 2007;14:262–8.
19. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis: Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, van Damme P, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS): revised report of an EFNS task force. Eur J Neurol. 2012;19:360–75.
20. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. J Neurol Neurosurg Psychiatry. 2003;74: 1258–61.
21. Chio A, Bottacchi E, Buffa C,Mutani R,Mora G; PARALS. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. J Neurol Neurosurg Psychiatry. 2006;77:948–50.
22. Zoccolella S, Beghi E, Palagano G, Fraddosio A, Guerra V, Lepore V, et al. ALS multidisciplinary clinic and survival: results from a population based study in southern Italy. J Neurol. 2007;254:1107–12.
23. Chiò A, Calvo A, Ghiglione P, Mazzini L, Mutani R, Mora G; PARALS. Tracheostomy in amyotrophic lateral sclerosis: a 10-year population based study in Italy. J Neurol Neurosurg Psychiatry. 2010;81:1141–3.
24. Bensimon G, Lacomblez L, Delumeau JC, Bejuit R, Truffinet P, Meininger V; Riluzole/ALS Study Group II. A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis. J Neurol. 2002;249:609–15.
25. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Lancet. 1996;347:1425–31.
26. Chiò A, Canosa A, Gallo S, Cammarosano S, Moglia C, Fuda G, et al. ALS clinical trials: do enrolled patients accurately represent the ALS population? Neurology. 2011; 77:1432–7.