diminished central motor output required to drive the respiratory muscles. Thus, the associated perceived effort required to generate a given ventilation during exercise is similarly reduced. The deeper, slower breathing pattern after radiation therapy and delay in the onset of tachypnoea reflect the recruitment of IC both at rest and during exercise as a result of lung volume deflation. Thus, the patient could increase tidal volume and ventilation during exercise to a greater extent than previously, before reaching critical mechanical constraints. For this reason, the onset of intolerable dyspnoea was delayed and the limits of tolerance extended.

Ventilatory requirements also decreased after radiation, presumably reflecting a net improvement in the ventilation–perfusion relationship. Thus, measurements of ventilatory inefficiency improved, reflecting more effective carbon dioxide elimination and reduced wasted ventilation. Arterial oxygen saturation was unaffected throughout exercise. The 27% reduction in $D_{L,CO}$ is a well-documented effect of radiation injury to the pulmonary vasculature and indicates a reduction in the surface area for pulmonary gas exchange.

The clinical decision to offer radical radiotherapy to individuals with severe COPD with early-stage lung carcinoma is often difficult given the known negative consequences of further erosion of an already limited ventilatory reserve. Given the vast pathophysiological heterogeneity of COPD, the impact of targeted radiotherapy is likely to be highly variable. It is conceivable, as our case illustrates, that in some patients with extensive lung hyperinflation and emphysema, radiation-induced alterations in the elastic properties of the lung and in ventilation–perfusion mismatching may actually have favourable effects on dyspnoea and exercise tolerance. Prospective studies to comprehensively characterise COPD phenotypes and measure the effects of radiation on respiratory physiology and patient-centred outcomes are required to better refine selection criteria for radiotherapy in this population.

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Linezolid safety, tolerability and efficacy to treat multidrug- and extensively drug-resistant tuberculosis

To the Editors:

Treatment of multidrug-resistant (MDR) tuberculosis (TB) (defined as *in vitro* resistance to at least isoniazid and rifampicin, the two most potent first-line drugs for TB treatment) and extensively drug-resistant (XDR)-TB (defined as *in vitro* resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the injectable drugs: amikacin, capreomycin or kanamycin) is still a major problem from both a clinical and a public health perspective [1–5].

Treatment outcomes for complicated MDR-TB cases (those with additional resistance beyond isoniazid and rifampicin) and XDR-TB cases being still poor, the need for information on the safety, tolerability and efficacy of other antibiotics that are potentially useful in their treatment is urgent [6–9].

TABLE 1	Sociodemographic and clinical characteristics of 16 multidrug-/extensively drug-resistant tuberculosis patients exposed to linezolid
XDR-TB	12/16 (75)
Drug resistance	
Streptomycin	15/16 (93.8)
Ethambutol	13/16 (81.3)
Pyrazinamide	15/16 (93.8)
Fluoroquinolones	16/16 (100)
Amikacin	7/16 (43.8)
Kanamycin	9/11 (81.8)
Capreomycin	16/16 (100)
Previous exposure to anti-TB therapy for >20 days	9/16 (56.3)
Number of times treated with anti-TB drugs for >1 month	1.5 (0–3)
Sputum smear converters	14/16 (87.5)
Culture converters	14/16 (87.5)
Duration of hospital stay days	82 (34–152)

Data are presented as n/N (%) or median (interquartile range). XDR-TB: extensively drug-resistant tuberculosis (TB).

In vitro and pharmacological data suggest that linezolid, an oxazolidinone antibiotic, could be useful in treating mycobacterial infections, including MDR-TB [9–11]. However, clinical experience with the off-label use of linezolid is still limited to case reports and small case series involving nontuberculous mycobacterial diseases [12] and TB, the four largest cohorts including 10 [13], 12 [14], 30 [15] and 85 cases (but only 45 with information on efficacy) [9], respectively. The aim of this study was to evaluate the safety, tolerability and efficacy of linezolid in a cohort of patients with MDR/XDR-TB from Portugal.

Clinical information necessary to study safety, tolerability and efficacy was prospectively collected on all MDR-TB cases treated with linezolid in Portugal between 2004 and 2009, with the exception of one case who started the treatment in 2003 (whose information was collected retrospectively). The protocol was designed to be compatible with that used to study the largest cohort available [9]. Internationally agreed outcome definitions were used [9].

In particular, a patient who completed treatment and was consistently culture-negative with at least five results for the final 12 months of treatment was defined as cured. If bacteriological results were lacking (*i.e.* <5 cultures performed), the case was defined as treatment completed. Treatment failure was defined as two or more positive cultures in the previous 12 months of treatment, or if a medical decision was made to terminate treatment due to poor response or adverse events. Definitions of other treatment outcomes (*i.e.* death, default and transfer) were the same as previously used in the European study on linezolid efficacy, safety and tolerability [9].

Approval for collection of study data was provided by the ethical committee of the coordinating centre [9], the participating hospitals complying with national regulations and organisational requirements for protection of human subjects. All data were coded and individual identifiers were available only to treating physicians.

Safety and tolerability end-points included major and minor side-effects. A major side-effect was defined as any adverse reaction that resulted in temporary or permanent discontinuation of linezolid, while a minor side-effect required only dose adjustment and/or addition of concomitant treatment.

Efficacy end-points included time to and proportion of sputum smear and culture conversions, and treatment outcome. Sputum conversion was defined as two consecutive negative sputum smears in patients who were sputum smear-positive at diagnosis. Time to culture conversion was defined as time from treatment start to date of the first of two consecutive negative cultures.

Drug susceptibility testing (DST) for all first- and second-line anti-TB drugs was performed by the Supranational Reference Laboratory in Porto, Portugal (quality-assured within the World Health Organization (WHO) proficiency scheme) [1, 2]. All participating centres performed sputum smear examinations weekly until negative, and then monthly. Cultures were performed monthly.

Regimens to treat MDR/XDR-TB cases were tailored to DST results according to WHO recommendations, using fluoroquinolones, injectable agents and other second-line oral agents co-administered with linezolid in all individuals. Linezolid was available without any limitation, and was prescribed at the dose of 1,200 mg once daily to 15 cases except one, who received 600 mg once daily.

The study end-points have been compared with those of the two largest series, including only patients with a definitive treatment outcome in the efficacy analyses (cure, failure and death) [9, 15].

Categorical variables were compared using the Chi-squared test and continuous variables by the t-test, or Wilcoxon–Mann–Whitney for unpaired data. A p-value of $\leqslant 0.05$ was considered statistically significant. Data were collected on standardised e-forms and analysed using Stata 9.0 (StataCorp, College Station, TX, USA).

The main results are summarised in table 1. 16 cases were analysed, 12 (75%) being affected by XDR-TB strains. 12 (75%) were males, with a mean±SD age of 34.8±10 yrs. Five (31.3%) were foreign-born immigrants (three from Cape Verde, one from Angola and one from Guinea-Bissau, respectively). Six (37.5%) were HIV seropositive, all of them being treated with anti-retroviral drugs. 12 (75%) of them were affected by pulmonary and four had simultaneous extrapulmonary forms (three pleural and one lymph node TB, respectively) of culture-positive disease. Three (18.8%) cases underwent surgical interventions (pleurectomy, lobectomy and pneumonectomy, respectively). The median duration of hospital stay in the cohort was 82 days (interquartile range (IQR) 34–152 days).

Out of 16 cases, nine completed their treatment (eight cured, one died), one defaulted at month 20 after achieving sputum smear and culture conversion, and six were still on treatment at the time of the analysis (four out of six having converted both sputum smear and culture after an average time of 275 and 650 days, respectively).

Linezolid was administered for a median (IQR) period of 375 days (270–630 days).

Three (18.8%) cases experienced adverse events, including anaemia, pancytopenia and polyneuropathy, after 30, 63 and 60 days of drug exposure, respectively.

Comparing the main outcomes with those of the main series (table 2), we observed no difference in successful treatment outcomes (89% in this study *versus* 80% in the European cohort [9] and 96% in the cohort of Schecter et al. [15], p-value not significant).

The median time to sputum smear and culture conversion was shorter in the European study than in the present study (76 *versus* 150 days, p=0.07; and 108 *versus* 180 days, p=0.02, respectively).

The proportion of major adverse events was significantly lower in Portugal than in the European cohort [9] (one out of 16 *versus* 27 out of 85; p=0.03) but not significantly different if compared with that recorded in the USA (one out of 16 *versus* three out of 30; p=0.65) [15].

TABLE 3	Anti-tuberculosis regimens prescribed to multidrug (MDR)-/extensively drug-resistant tuberculosis (TB) patients in Portugal, 2003–2009				
Patient	**Anti-TB regimen**	**Sputum smear conversion days**	**Sputum culture conversion days**	**Linezolid exposure days**	**Anti-TB treatment exposure from beginning MDR-TB treatment months**
1	CS, LZD, PAS, PZA	365	1460	570	60
2	AMK, Cl, CS, LZD, MFX, PAS		105	240	11
3	AMK, CS, LZD, MFX, PAS	120	160	330	11
4	CM, CS, EMB, LZD, MFX, PAS	540	800	690	35
5	CS, Clof, LZD, MFX, PAS	60		120	9
6	AM/CA, Cl, CS, LZD, MFX	75	180	840	28
7	AMK, Cl, Clof, LZD, MFX, RB	1380	1380	330	71
8	AMK, Clof, EMB, LZD	312	312	720	24
9	AMK, CS, LZD, MFX, PAS	39	39	300	10
10	Cl, CS, LZD, MFX, PAS	60	60	180	22
11	AMK, Cl, LZD, MFX, PAS	1800	1800	300	84
12	CS, LZD, MFX, PAS	180	180	490	26
13	AMK, Cl, LZD, MFX, PAS			510	18
14	CS, Cl, LZD, MFX	30	30	420	24
15	AMK, Cl, CS, EMB, LZD, MFX	90	90	240	27
16	Cl, CS, EMB, LZD, MFX	1443	1443	803	65

CS: cycloserine; LZD: linezolid; PAS: p-aminosalicylic acid; PZA: pyrazinamide; AMK: amikacin; Cl: clarithromycin; MFX: moxifloxacin; CM: capreomycin; EMB: ethambutol; Clof: clofazimine; AM/CA: amoxicillin/clavulanic acid; RB: rifabutin.

No significant difference was found when the comparison for minor adverse events was performed.

The regimens used to treat individual patients and information on bacteriological conversion are summarised in table 3.

The results of this observational study confirm that under specialised management, treatment success in difficult-to treat MDR-/XDR-TB cases is high, although the proportion of XDR-TB cases (and of HIV-positive) individuals in Portugal is higher than in the other major studies available [9, 15]. Furthermore, a control group of MDR-/XDR-TB patients treated with linezolid-sparing regimens was not analysed. However, the proportion of adverse events (both minor and major) was lower than in previous cohorts, being significant only when comparing major adverse events of the Portuguese cohort *versus* a European one [9], although a relatively high dose of linezolid (1,200 mg once daily) was used.

The evaluation of safety and tolerability is difficult to perform, as different drugs are included in the treatment regimens (necessarily guided by DST) and the duration of exposure to linezolid, as well as the dosages prescribed (300–1,200 mg), varied among patients and among studies.

Pending larger studies, a meta-analysis including individual data from the patients treated with linezolid will be important to hopefully give the final word on whether this drug could really be considered for wider use outside the few cases affected by strains resistant to more than seven drugs [9].

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