A randomised phase III study of 72 hour infusional versus bolus bleomycin in BEP (bleomycin, etoposide and cisplatin) chemotherapy to treat IGCCCG good prognosis metastatic germ cell tumours (TE 3)

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Abstract

Background: Bleomycin is an integral part of combination chemotherapy in germ cell tumours. Pulmonary symptoms often dictate drug cessation and death occurs in 1-2% of patients. Circumstantial evidence suggests that continuous infusion may be less toxic.

Methods: We conducted a randomized phase 3 study to see whether infusional bleomycin was associated with less pulmonary toxicity. Two hundred and twelve patients were randomized to receive either conventional BEP with weekly bleomycin (30000 units /week IV over 30min) or the same doses but administered as a 90000 unit infusion on day 1 over 72 hours. The primary endpoint was CT proven lung toxicity, secondary endpoints included PFS and changes in lung function testing. Repeated measures mixed effects model was used to analyse the data.

Results: There was no difference between the two arms for CT assessed lung toxicity (difference=1.4, p=0.92, CI:-0.36, 3.16) but only older patients (Age>30) had significantly higher toxicity (Difference=4.81, CI: 3.04, 6.58). There was a trend for increasing toxicity after 1 cycle and subsequently at end of treatment and 1 year ($p \leq 0.002$). Toxicity level was the highest at the end of treatment. Lung function testing between the two arms failed to show any differences, and did not predict for subsequent lung damage. The median follow-up was 2.5 years. Two-years PFS rate was 93% in both arms (hazard ratio (infusion vs conventional) was 0.91; 95% CI 0.33 to 2.52). Cough but not shortness of breath was associated with CT evidence of bleomycin toxicity.

Conclusion: Infusional bleomycin does not have any advantage over standard administration of bleomycin in patients with good prognosis germ cell tumours. The study supports the abandonment of routine pulmonary function testing, instead seeking the presence symptoms especially cough and the early use of CT scanning of the chest to evaluate potential lung toxicity.

Introduction

The treatment of metastatic germ cell tumours has changed with the realisation that most patients with low risk disease (IGCCCG- good prognosis) with 3 cycles of cisplatin, etoposide and bleomycin (BEP). Randomised studies have confirmed that cisplatin100mg/m2, etoposide 500mg/m2 and bleomycin 90,000 units per cycle is optimal. The cisplatin and etoposide may be given over 3 or 5 days (1) and reductions in the bleomycin or etoposide are associated with poorer overall survival (2). The omission of bleomycin leads to lower survival (3). Bleomycin has long been known to cause unpredictable and occasionally fatal lung toxicity with the suggestion that prior poor lung function, a smoking history, and impaired renal function predispose to an increased likelihood of toxicity (4). Retrospective reports have suggested that the damage caused by bleomycin is related to the peak levels of the drug and that this may be avoided by giving the drug as a continuous infusion (5). In vivo experiments in animal models have supported the hypothesis that pulmonary toxicity may be reduced and efficacy increased by this approach (6).

In a patient group with a very good outcome, optimisation of bleomycin might be expected to improve efficacy and reduce toxicity. As the value of pulmonary function testing in this setting has been controversial (7) we wished to see whether pre- treatment pulmonary function testing could identify an at risk population for development of lung toxicity and also whether changes during treatment correlated with the development of CT scan changes. We also wished to see whether any symptoms associated with the development of bleomycin induced lung injury e. g. shortness of breath, cough, and chest discomfort correlated with CT changes.

In order to quantify the amount of damage on CT we chose to use a modification of the CT scoring system described by Rimmer et al (8) each lung was split in to axial segments and the amount of scarring in each quadrant (right anterior, right posterior, left anterior, left posterior) was quantified leading to a summed score allowing the percentage of lung involvement to be determined and the degree of severity of the changes also to be described.

A randomised trial was therefore designed for patients with IGCCCG good prognosis disease - in each arm cisplatin and etoposide doses and delivery were identical – in one arm patients were to receive bleomycin in a conventional fashion (30, 000units intravenously over 30 minutes) on days 1, 8 and 15 of a 21 day cycle, in the other patients received an intravenous continuous infusion of bleomycin (90,000units over 3 days) on days 1, 2 and 3 also repeated every 21 days.

Patients and Methods

Patients were males with IGCCCG good prognosis disease (testicular germ cell tumours with metastases but no non-pulmonary visceral sites with tumour markers not exceeding the following AFP< 1000ng/ml, hCG, 5000 iU/ml, LDH < 1.5x the upper limit of normal) were eligible.

They were staged using CT scanning. High resolution CT of chest was not used to evaluate lung damage – rather it was assessed on the basis of conventional lung settings. They were required to have adequate renal function (calculated or measured glomerular filtration rate of > 50ml/min). Patients were randomised to receive 3 cycles of 3 day BEP (cisplatin 50g/m2 on day 1 and 2, etoposide 166mg/m2 day 1,2 and 3) and either conventional bleomycin 30,000 units per week on days 1, 8 and 15 as a 30min intravenous infusion (short arm of study) or a protracted infusion (90,000 units as a continuous intravenous infusion over 3 days on days 1, 2 and 3 of each cycle (long arm of study). A Chest CT was performed on day 21 of the 1st cycle , at the end of treatment (12 weeks after chemotherapy started) 1 year and 2 years after treatment. Quality of life assessments were performed prior to treatment, prior to the second cycle, at the end of treatment, 1 year and 2 years following therapy. The EORTC QLQC-30 questionnaire with the addition of the LC 17 questionnaire (with specific questions about respiratory symptoms was used a questionnaire – originally developed for lung cancer supplemented to look for specific questions attributable to lung toxicity changes (with detailed questions regarding the presence or absence of cough as well as the degree of shortness of breath).

The primary end point of the study was the development of CT detected lung changes attributable to bleomycin. The secondary endpoints were progression-free survival, overall survival, changes in pulmonary function testing, and quality of life. Pulmonary function tests were performed prior to treatment, at day 21 of the first cycle, at the end of treatment, 1 year and 2 years post treatment. These included an assessment of FEV1, FVC, TlCO and KCO.

Patients were required to give written informed consent. The trial had formal ethical approval (trial reg MREC 3/3/029).

CT review

All the CT scans were anonymised, the reporting radiologist was blinded to treatment allocation and all scans were viewed by a single radiologist. The scans were reported as follows. Axial scans through the lung fields were obtained every 5mm. Each lung filed was split into an anterior and posterior section (4 in all- right anterior, right posterior, left anterior and left posterior). At the lung bases some sections were not present due to the curvature of the diaphragm. The degree of damage was graded between 0-3.Grade 1 changes represented mild sub-pleural opacification, grade 2 changes – more extensive than grade 1 but no coalescence. Grade 3 diffuse change with coalescence. The number or total sections for each scan examined was noted allowing a percentage of sections with involved changes to be derived as well as the proportion of grade 2 and 3 changes. The results were summarised in the following format –the percentage of sections showing any damage, the number of sections showing individually grade1, 2 or 3 damage. This was carried out at baseline, day 21, end of treatment and 1 and 2 years post treatment.

Statistics

Sample size of 212 was calculated to detect a difference of 16% Bleomycin damage with 80% power at the 5% level of significance using 2-sided test. A previous retrospective review of the toxicity encountered when bleomycin was administered as a continuous infusion had suggested a substantial reduction in bleomycin induced changes -0n the basis of this a study of 46 patients would have been needed to confirm this difference. The study was there powered as a phase III study. An initial review after 46 patients suggested no significant difference between the two arms and therefore the study was continued to its full recruitment.

Two hundred and twelve patients were randomised between the two arms according to 1:1 allocation. Patients were stratified for smoking (smoker vs non-smoker), renal dysfunction (greater than or less than or equal to 80ml/min as calculated by Cockroft and Gault. and age (<30 vs 30 or more) as all factors have been associated with an increased risk of bleomycin induced lung changes.

To determine the statistical significance of the association between categorical and continuous outcome variables, the Chi-square and Independent samples T-test were used as appropriate (Table 1). Chi Square test used to calculate P values for age category, smoking status and creatinine clearance. Independent samples T test used to calculate P values for baseline toxicity, age and follow-up.

Repeated measures mixed effects models are used to model CT proven lung toxicity as a function of the predictor variables accounting for both fixed and random effects. Fixed effects included the stratification factors, such as age and smoking status; whereas random effect was patient ID.

Nonparametric test for trend was carried out to observe for trends in toxicity grading with time. Pearson's correlation coefficients were obtained to assess correlation between lung function variables and lung toxicity at each time point.

Results

The CONSORT diagram for study design and randomisation is shown in Figure 1. Base line characteristics are shown in Table 1.

Table 1 confirms the validity of randomization with the two groups well balanced in terms of baseline characteristics. Thirty-five percent of patients were smokers, 5% had an estimated GFR of < 80ml/min and 53% were over the age of 30.

Figure 1: Consort diagram for showing study population

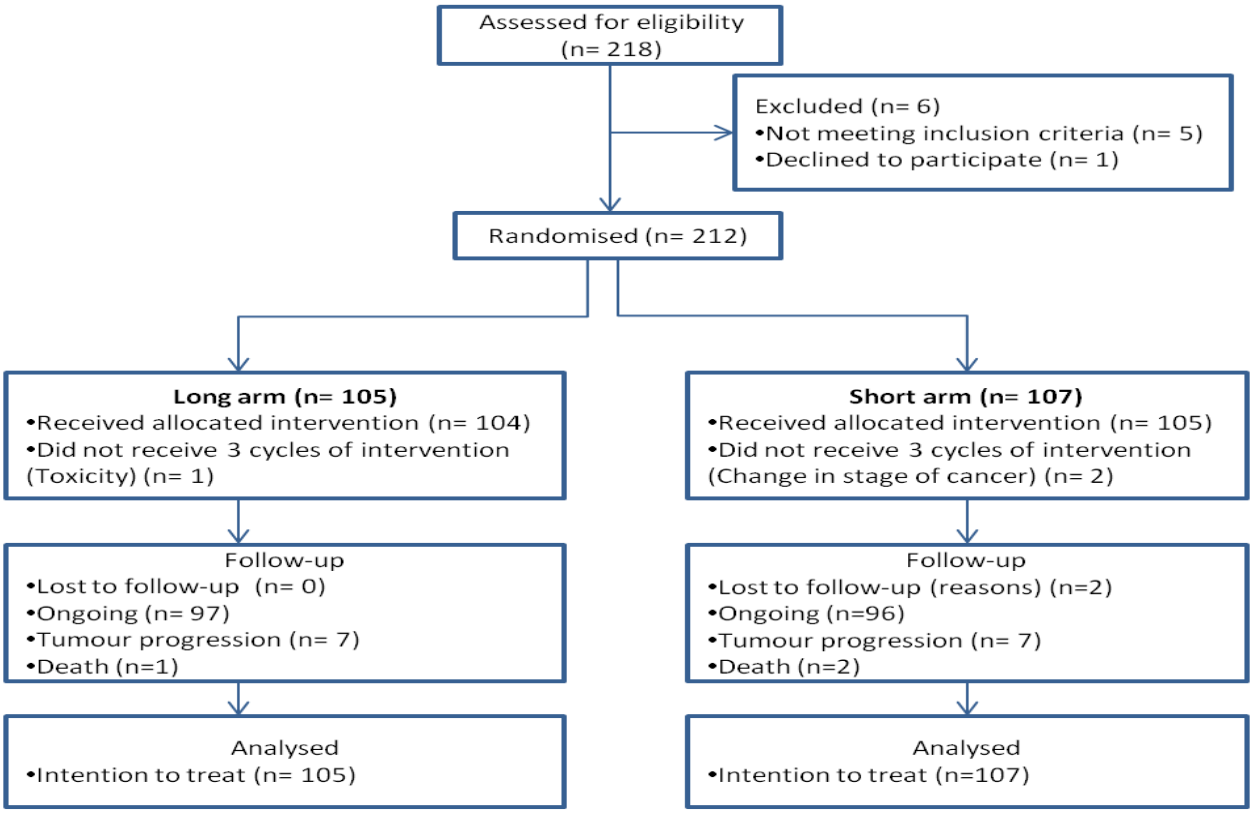

Table 1. Baseline characteristics of study patients

Baseline characteristics	Long arm (N= 105)		Short arm (N= 107)	
	n	%	n	%
Baseline toxicity (mean (SD))*	0.89 (4.5)		0.78 (2.5)	
Age (years)				
<=30	49	46.7	51	47.7
>30	56	53.3	56	52.3
Age (years) (median (IQR))	31.5 (26.5, 36.0)		31.5 (24.8 , 39.1)	
Follow-up (years) (median (IQR))	2.3 (1.9, 3.7)		2.3 (2.1, 3.5)	
Smoking status				
Non-smoker	67	63.8	71	66.4

Smoker	38	36.2	36	33.6
Creatinine clearance				
<=80 ml/min	7	6.7	4	3.7
>80 ml/min	98	93.3	103	96.3

* % of grade 1 or above toxicity at baseline

The median follow-up was 2.3 years. Two-years PFS rate was 93% in both arms (hazard ratio infusion versus conventional was 0.91; 95% CI 0.33 to 2.52).

32% of patients had evidence of damage by day 21 and by the end of the treatment 69% had evidence of lung damage.Two percent of patients had evidence of grade 2 toxicity at day 21 but by the end of the treatment 34.5% had grade 2 toxicity. Of those who showed no evidence of lung damage at day 21, 27% went on to develop grade 2 lung damage at end of treatment (33% of long arm patients versus 22% short arm).]

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Those patients with smaller body surface areas (< median) showed no evidence of increased toxicity despite the fact that dosing was fixed independently of body size.

There was a trend for increasing toxicity after 1 cycle and subsequently at end of treatment and 1 year ($p \leq 0.002$). The pattern of damage was that it peaked at the end of treatment with it subsequently falling by 1 and 2 years. [At day 21 of treatment 31% of patients in the long arm had grade 1 or above toxicity compared to 27% in the short arm. At the end of treatment the results were 80% vs. 62% respectively and at one year post treatment 54% vs. 51%.]

At day 21 of treatment 4% of patients in the long arm had grade 2 or above toxicity compared to 0% in the short arm. At the end of treatment the results were 45% vs. 25% and at one year post treatment 4% vs. 5% respectively.

Table 2. Repeated measures mixed effects models of levels of lung toxicity

	% of Grade 1 or above toxicity		% of Grade 2 or above toxicity		% of Grade 3 toxicity	
	Difference	95% CI	Difference	95% CI	Difference	95% CI
Treatment						
Short arm	*ref*	-	*ref*	-	*ref*	-
Long arm	1.4	-0.36, 3.16	0.92	0.22, 1.62	0.05	-0.11, 0.22
Baseline toxicity	0.67	0.40, 0.94	0.16	0.04, 0.28	0.002	-0.03, 0.03
Age (years)						
<=30	*ref*	-	*ref*	-	*ref*	-
>30	4.81	3.04, 6.58	0.84	0.14, 1.55	0.14	-0.03, 0.30

Smoking status						
Non-smoker	*ref*	-	*ref*	-	*ref*	-
Smoker	0.49	-1.36, 2.34	0.06	-0.68, 0.79	0.11	-0.06, 0.28
Creatinine clearance						
<=80 ml/min	*ref*	-	*ref*	-	*ref*	-
>80 ml/min	-0.79	-5.26, 3.68	0.15	-1.58, 1.88	-0.03	-0.44, 0.38
CT scan visit						
Day 21	*ref*	-	*ref*	-	*ref*	-
End of treatment	7.28	5.50, 9.06	2.25	1.55, 2.96	0.17	-0.002, 0.33
1 year post treatment	2.18	0.38, 3.98	0.08	-0.63, 0.79	-0.01	-0.18, 0.16
2 year post treatment	2.14	0.14, 4.14	-	-	-	-

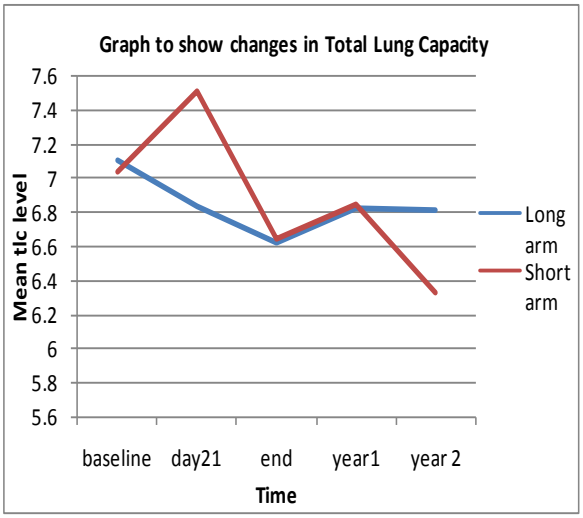
Repeated measures mixed effects analysis, Table 2, shows that there was no significant difference (95% Confidence Interval includes zero) in percentage of grade 1 and above toxicity between the two arms (diff in percentage of grade 1 or above toxicity 1.4; 95% CI: -0.36, 3.16). A significantly higher level of grade 2 and above toxicity was observed in the infusion arm (0.92; 0.22, 1.62) mainly at the end of treatment.

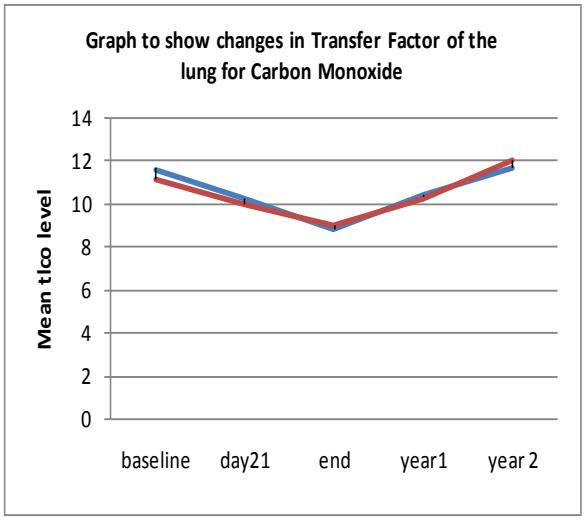
As baseline toxicity increases by 1 unit, the percentage of grade 1 or above toxicity decreases by a factor of 0.67. Similarly, if baseline toxicity increases by 1 unit, the percentage of grade 2 or above toxicity decreases by a factor of 0.16. Of the stratified factors only age was statistically significant. Patients older than 30 had 4.8 times higher grade 1 or above toxicity but 0.84 times lower grade 2 or above toxicity. Smoking was not associated with baseline damage (P = 0.46), nor was it related to the severity and frequency of subsequent bleomycin toxicity (Table 2).

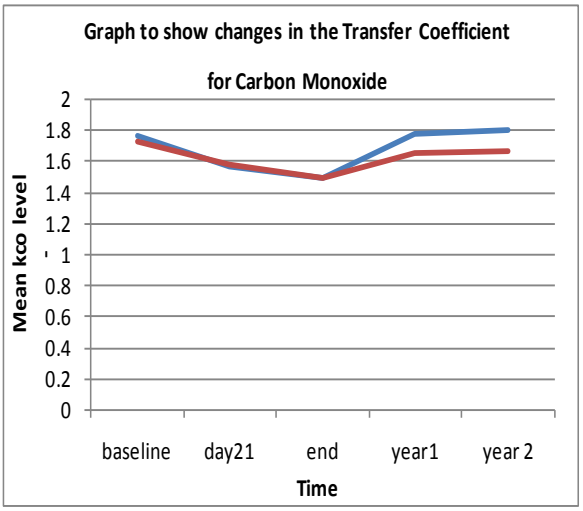
Lung function and toxicity:

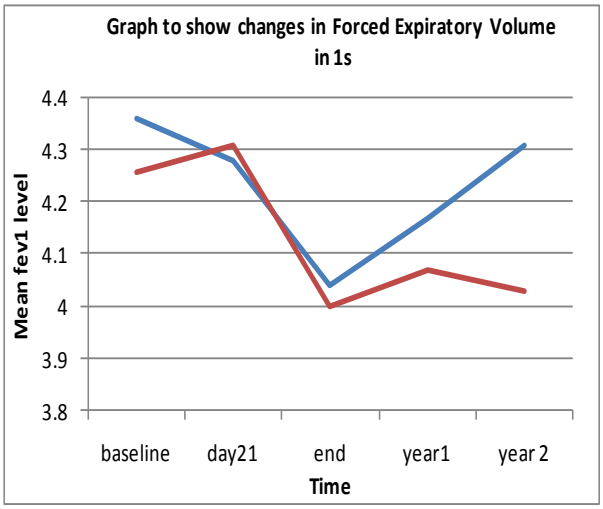
There was no relationship between pre-existing lung function and subsequent toxicity (see Figure 2). Pulmonary function declined during treatment and then recovered 1 year post therapy.

Figure 2. Trend in toxicity based on lung function tests by arm


Graph to show changes in Total Lung Capacity
Mean tlc level
7.6
7.4
7.2
7
6.8
6.6
6.4
6.2
6
5.8
5.6
baseline
day21
end
year1
year 2
Time
Long arm
Short arm


Graph to show changes in Transfer Factor of the lung for Carbon Monoxide
Mean tlco level
14
12
10
8
6
4
2
0
baseline
day21
end
year1
year 2


Graph to show changes in the Transfer Coefficient for Carbon Monoxide
Mean kco level
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
baseline
day21
end
year1
year 2
Time


Graph to show changes in Forced Expiratory Volume in 1s
Mean fev1 level
4.4
4.3
4.2
4.1
4
3.9
3.8
baseline
day21
end
year1
year 2
Time

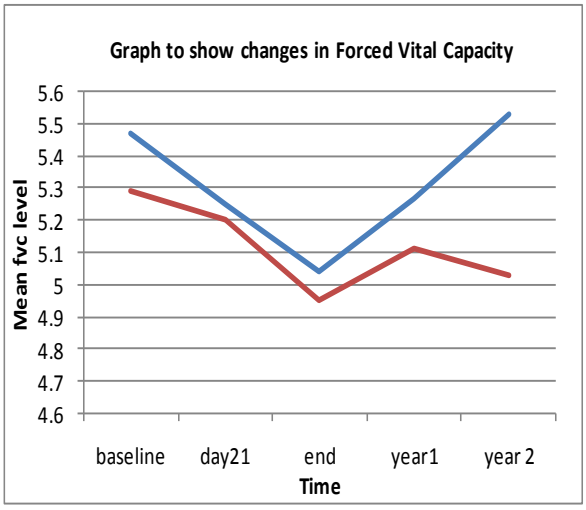

Graph to show changes in Forced Vital Capacity
Mean fvc level
5.6
5.5
5.4
5.3
5.2
5.1
5
4.9
4.8
4.7
4.6
baseline
day21
end
year1
year 2
Time

Table 3. Correlation between lung function and lung toxicity

Lung function test		Grade 1 and over lung toxicity					
		Baseline		End of treatment		One year post treatment	
		r	P	r	P	r	P
Baseline	fvc	0.03	0.71				
	fev1	0.01	0.89				
	tlc	0.03	0.79	-	-	-	-
	tlco	-0.07	0.45				
	kco	-0.07	0.40				
End of treatment	fvc			**-0.32**	**<0.001**		
	fev1			**-0.36**	**<0.001**		
	tlc	-	-	-0.19	0.06	-	-
	tlco			**-0.35**	**<0.001**		
	kco			**-0.20**	**0.02**		
One year post treatment	fvc					-0.17	0.11
	fev1					-0.17	0.11
	tlc	-	-	-	-	-0.07	0.58
	tlco					**-0.21**	**0.04**
	kco					-0.04	0.72

Table 3 shows that lung function and toxicity are correlated only at the end of treatment (P <0.05). Further analysis shows that pre-treatment lung function doesn't predict subsequent development of pulmonary toxicity (all CIs includes 0); (Table 4).

Table 4. Association between pre-treatment lunch function and end of treatment toxicity

	% of Grade 1 or above toxicity		*% of Grade 2 or above toxicity*		*% of Grade 3 toxicity*	
	Difference	***95% CI***	***Difference***	***95% CI***	***Difference***	***95% CI***
Baseline fvc	***-0.45***	***-3.08, 2.18***	***-0.62***	***-1.84, 0.61***	***-0.01***	***-0.16, 0.23***
Baseline fev1	***-2.58***	***-5.80, 0.63***	***-1.1***	***-2.61, 0.40***	***0.12***	***-0.18, 0.41***
Baseline tlc	***0.28***	***-2.14, 2.70***	***-0.17***	***-1.30, 0.95***	***-0.05***	***-0.31, 0.20***
Baseline tlco	***-0.61***	***-1.79, 0.58***	***-0.46***	***-1.02, 0.09***	***0.01***	***-0.10, 0.13***
Baseline kco	***-3.93***	***-11.94, 4.07***	***-1.74***	***-5.51, 2.03***	***0.02***	***-0.74, 0.78***

Quality of Life (see table 5)

The quality of life data showed that the development of a dry cough rather than shortness of breath and chest tightness was the only symptom associated with the development of CT lung toxicity. However,

shortness of breath showed a positive trend (p=0.09) for the association with the development of CT lung toxicity.

Table 5. Association between symptoms and lung toxicity

Symptoms	Mean G1 or greater % lung toxicity			Mean G2 or greater % lung toxicity		
	Better or no change	Worse	P	Better or no change	Worse	P
Cough	8.3	17.3	**0.001**	1.8	5.9	**0.002**
Cough up mucus	10.4	13.3	0.33	3.0	3.4	0.77
cough up blood	-	-	-	-	-	-
Tightness in chest	10.7	12.2	0.61	2.6	4.5	0.18
SOB at rest	12.0	7.2	0.16	3.7	0.7	0.09
SOB on walking	11.1	11.4	0.91	3.2	2.9	0.84
SOB on climbing stairs	10.4	12.9	0.36	3.0	3.4	0.81

Discussion

Continuous infusion in comparison to bolus application has been postulated to be associated with increased antitumour activity and decreased toxicity, particularly pulmonary fibrosis. In stark contrast however, a continuous infusion of 90 000 units of bleomycin over 72 hours was unable to reduce the likelihood of developing pulmonary toxicity over the conventional administration of 30 000 units by short weekly infusion per week. In fact there was significantly higher level of grade 2 and above toxicity in patients in the infusion arm. The conclusion of this study is therefore to reject the hypothesis nevertheless it has expanded our knowledge as to the timing of development of lung toxicity and the natural history of how it resolves. It is possible that a more prolonged infusion may have been able to reduce toxicity. In addition there was no suggestion that efficacy was increased by this approach despite evidence from animal models suggesting otherwise. Supporting this conclusion, an in vivo study based on heterotransplanted testicular cancer cell lines found no significant difference in antitumour activity between continuous or bolus application of Bleomycin when the same cumulative doses were compared. Neither was there any difference with respect to bleomycin toxicity upon histological examination (9).

Pulmonary toxicity from bleomycin may be related to peak levels and one weakness of this study was failure to measure end of infusion peak levels – it may be that the infusion produced higher levels than we had anticipated. As the dosing of bleomycin was fixed those patients with smaller body surface areas were getting comparably higher doses – despite this there was no evidence that patients with a smaller body surface area were more likely to develop bleomycin induced lung changes.

This was a pragmatic study – high resolution CT scanning was not used to assess pulmonary toxicity on the basis that we were not looking for a test to be more sensitive but wanted to assess clinically more relevant changes.

The finding of changes, starting at day 21 progressing until the end of treatment and then regressing , offers an opportunity for using early changes as a warning that more severe damage may occur if the bleomycin is continued. This may be particularly important as many of the factors associated with subsequent pulmonary toxicity were not borne out in this study. With the exception of age and baseline toxicity neither smoking history nor renal function predicted toxicity. In the case of renal function, most (92%) had an estimated glomerular filtration rate of > 80ml/ min so although no association was noted it may simply suggest that only significantly impaired renal function increased bleomycin toxicity . In the case of smoking history, however, there were a large number of smokers and this certainly supports the view point that smoking history per se is not a contra –indication to bleomycin use.

Bleomycin lung toxicity remains unpredictable and can be fatal in a curable illness this can lead to dropping bleomycin to avoid this effect. Yet the evidence that omission of bleomycin can be safely done in this patient group with the addition of a further cycle of cisplatin and etoposide is not as strong as many have suggested. For 3 cycles of cisplatin and etoposide the absence of bleomycin was associated with a poorer survival (10).

It remains questionable as to whether dropping bleomycin can be compensated for by the addition of a 4^{th} cycle of cisplatin and etoposide. One study – underpowered to show a survival difference showed a 5% higher event rate in patients randomized to 4 cycles of cisplatin and etoposide (11).

Pulmonary function testing was not of use in this study in the identification of patients at risk of developing lung toxicity. It was stipulated in the study that no reductions for asymptomatic changes in pulmonary function testing should be made. This is not the first time that the value of pulmonary function testing has been questioned (8). This argues for the abandonment of routine pulmonary function testing. This may avoid patients having their bleomycin omitted in the first place – in addition it will help avoiding unnecessary stopping or substitution of bleomycin thus paradoxically helping patients. Thus early CT scanning after 1 cycle of treatment rather than pulmonary function testing or smoking history was best able to identify patients at risk of subsequent lung toxicity. Absence of grade 2 toxicity at this point means significant toxicity is unlikely to develop during the final two cycles.

The symptom assessment questionnaire showed that cough rather than shortness of breath is the most important symptom that should be sought before administration of bleomycin and if this is noted in the absence of another cause should lead to an early CT of the chest to establish if pulmonary toxicity has occurred.

The number of treatment failures in each arm (6%) was less than seen in previous randomised studies in this population (1, 2) despite the fact that the median age group was higher (32 y) than in comparable studies. The low level of treatment delays and drug omissions may have been responsible for this. It is important to point out that the overall prevalence of bleomycin induced lung damage was

relatively low and this is in part due to the fact that the study only included patients with IGCCCG good prognosis disease. In patients with more pulmonary disease where the doses of bleomycin will be greater, risks are likely to be higher. In a review by Sullivan et al (4) of patients treated, 7% had bleomycin induced changes age, dose (> 300, 000 units) and renal dysfunction were associated with increased risk of damage.

In conclusion bleomycin induced lung damage in patients with good prognosis germ cell tumours occurs independent of the method of delivery. The study supports the abandonment of routine pulmonary function testing both to identify patients at risk and using deterioration in pulmonary function tests a reason to stop or attenuate bleomycin dosing. Instead, seeking the presence symptoms especially cough and the early use of CT is a preferred approach. A history of smoking is not a reason to withhold bleomycin either. Whether these findings extend to patients with more advanced disease remains undetermined.

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ECMC, participating patients etc.CRUK, orchid

References

1. de Wit R, Roberts JT, Wilkinson PM, de Mulder PH, Mead GM, Fossa SD, et al. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol. 2001;19(6):1629-40.
2. Toner GC, Stockler MR, Boyer MJ, Jones M, Thomson DB, Harvey VJ, et al. Comparison of two standard chemotherapy regimens for good-prognosis germ-cell tumours: a randomised trial. Australian and New Zealand Germ Cell Trial Group. Lancet. 2001;357(9258):739-45.
3. Loehrer PJ, Sr., Johnson D, Elson P, Einhorn LH, Trump D. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. J Clin Oncol. 1995;13(2):470-6.
4. O'Sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol. 2003;14(1):91-6.
5. Cooper KR, Hong WK. Prospective study of the pulmonary toxicity of continuously infused bleomycin. Cancer Treat Rep. 1981;65(5-6):419-25.
6. Sikic BI, Collins JM, Mimnaugh EG, Gram TE. Improved therapeutic index of bleomycin when administered by continuous infusion in mice. Cancer Treat Rep. 1978;62(12):2011-7.
7. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH. Decrease in pulmonary function during bleomycin-containing combination chemotherapy for testicular cancer: not only a bleomycin effect. Br J Cancer. 1995;71(1):120-3.
8. Rimmer MJ, Dixon AK, Flower CD, Sikora K. Bleomycin lung: computed tomographic observations. Br J Radiol. 1985;58(695):1041-5.
9. Bokemeyer C, Ludwig E, Reile D, Harstrick A, Poliwoda H, Schmoll H. Antitumor-activity and toxicity of continuous-infusion versus bolus administration of bleomycin in 2 heterotransplanted human testicular cancer cell-lines. Oncol Rep. 1995;2(1):161-5.
10. de Wit R, Stoter G, Kaye SB, Sleijfer DT, Jones WG, ten Bokkel Huinink WW, et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. J Clin Oncol. 1997;15(5):1837-43.
11. Culine S, Kerbrat P, Kramar A, Theodore C, Chevreau C, Geoffrois L, et al. Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol. 2007;18(5):917-24.