EUROPEAN JOURNAL OF CANCER 45 (2009) 2234–2235

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Editorial Comment

Palliative chemotherapy: Do we need yet another end-point?

Jan P. van Meerbeeck[a,*], *Paul Baas*[b]

[a]*Lung Oncological Network Gent (LONG), Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium*
[b]*Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands*

ARTICLE INFO

Article history:
Received 15 May 2009
Accepted 19 May 2009
Available online 11 June 2009

In a disease with a prevalence as high as observed in advanced non-small cell lung cancer (NSCLC), the benefit of a novel palliative treatment is typically demonstrated by an improvement in survival that is balanced against the treatment-induced morbidity, as any intervention has its risk of toxic side-effects. The smaller the benefit, the more difficult this trade-off becomes. Patient-related outcomes (PROs) are used whenever benefit and risk are to be aligned. Reporting toxicity has been graded and standardised by the use of Common Terminology Criteria for Adverse Events (CTCAEs), developed by the National Cancer Institute.[1] Opinions differ whether toxicity scoring by investigators is sufficiently representative of the patient's qualitative perspective of benefit or harm and whether it should not be complemented by one or more aspects of patient health status, e.g. Quality of Life (QoL). QoL is considered to be a multi-domain concept with physical, psychological, emotional and social components, that is increasingly used in phase 3 trials. Recently, the current standards for analysing aspects relating to QoL or symptom control in randomised controlled trials were reviewed and found to be poor.[2]

In this issue, Scagliotti et al. report on a novel end-point for weighting the clinical benefit-risk of a first-line chemotherapy regimen in advanced non-small cell lung cancer (NSCLC)[3]: survival-without-toxicity is defined as the interval between the date of randomisation to the first date of any grade 3 or 4 toxicity (regardless of drug causality) or death from any cause. This end-point was first coined by Pujol et al. in an unplanned post-hoc analysis of a randomised phase 3 trial comparing docetaxel and pemetrexed in pretreated NSCLC patients.[4] There was no difference in overall efficacy and a clinical benefit was attributed to pemetrexed because of its lower rate of clinically important grade 3 and 4 toxicities: neutropaenia lasting longer than 5 days, febrile neutropaenia, documented infections related to neutropaenia, anaemia, thrombocytopaenia, fatigue, nausea, vomiting, diarrhoea, stomatitis and neurosensory events.

Recently, Scagliotti et al. reported an equivalent efficacy of a novel cisplatin/pemetrexed combination and a cisplatin/gemcitabine standard in a large randomised phase 3 trial in patients with advanced NSCLC.[5] Less grade 3 and 4 toxicity was observed with pemetrexed in the overall analysis and a pre-planned subgroup analysis showed a significant improvement in outcome in the large cohort of patients with non-squamous histology treated with the experimental regimen (Table 1). Safety within both histology groups was reportedly generally consistent with the overall safety results. QoL data were not collected and pemetrexed was approved by both United States (US) and European registration authorities as first-line treatment of advanced non-squamous NSCLC in combination with cisplatin, based on the results of this subgroup analysis.

The present *unplanned* subgroup analysis of the same patients of the registration trial shows that the combination of cisplatin and pemetrexed improves survival-without-toxicity in both the whole group of patients and the cohort with

* *Corresponding author:* Tel.: +32 92402611; fax: +32 93322341.
E-mail address: Jan.vanmeerbeeck@ugent.be (J.P. van Meerbeeck).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.05.020

Table 1 – Clinically important grade 3–4 toxicities and median outcome by treatment arm in all patients and per histological type.

	Treatment arm	Overall	1000 Patients with non-squamous histology	473 Patients with squamous histology
Safety [5]		% Patients/treatment arm		
Febrile neutropaenia	Cisplatin–gemcitabine	3.7% of 830	Not different from the overall safety analysis	Not different from the overall safety analysis
	Cisplatin–pemetrexed	1.3% of 839		
Anaemia	Cisplatin–gemcitabine	9.9% of 830		
	Cisplatin–pemetrexed	5.6% of 839		
Thrombocytopaenia	Cisplatin–gemcitabine	12.7% of 830		
	Cisplatin–pemetrexed	4.1% of 839		
Fatigue	Cisplatin–gemcitabine	4.9% of 830		
	Cisplatin–pemetrexed	6.7% of 839		
Nausea	Cisplatin–gemcitabine	3.9% of 830		
	Cisplatin–pemetrexed	7.2% of 839		
Vomiting	Cisplatin–gemcitabine	6.1% of 830		
	Cisplatin–pemetrexed	6.1% of 839		
Outcome		Median (months)		
Overall survival [5]	Cisplatin–gemcitabine	10.3	10.4	10.8
	Cisplatin–pemetrexed	10.3	11.8	9.4
Survival without toxicity [3]	Cisplatin–gemcitabine	2.8	2.8	2.9
	Cisplatin–pemetrexed	5.6	5.9	4.1

non-squamous histology. The authors report a similar effect on 'a selection of the most clinically relevant drug related grade 3 or 4 toxicities', but do not provide figures (Table 1). Neither the rate of grade 3–4 toxicities nor the survival-without-toxicity was different among the patients with squamous histology, treated with either drug regimen. The authors ascribe this to a histologically based treatment effect of pemetrexed on survival, rather than a safety advantage of the cisplatin–pemetrexed combination over the cisplatin–gemcitabine one.

Does this novel end-point improves our interpretation of clinical risk-benefit? Since both chemotherapy regimens have different toxicity rates, it can be expected that this difference will translate in a different time-to-toxicity, as in this report. When however treatments with different time-to-toxicity windows are compared, the introduction of an analytic bias is inevitable. Furthermore, some of the observed toxicities do not necessarily translate in severe clinical toxicities. Including these 'paper' toxicities in a survival-without-toxicity analysis is likely to overestimate the magnitude of the end-point. Finally, in as much as death by any cause is included in the definition of survival without toxicity, it cannot be excluded that a difference in cancer deaths drives the figures and that the proposed definition becomes a weak surrogate for overall survival. The proposed end-point could gain in accuracy by restricting to clinical toxicities and excluding non-toxic deaths. It is likely to be only useful for comparing treatments with a different toxicity profile and a similar time-to-toxicity window.

Where do we go from here? There is undoubtedly a need for a more refined but pragmatic tool to correlate risk and benefit of palliative chemotherapy. In their article, Joly et al. propose a number of recommendations to improve current QoL reporting.[2] Whether survival without toxicity is clinically relevant needs further validation, by analysing it as a pre-planned end-point in prospective-randomised trials, using other drugs than pemetrexed, in other tumour types than NSCLC and including individualised QoL analysis.

Conflict of interest statement

Dr. Jan van Meerbeeck received honoraria from Eli Lilly, sanofi-aventis, GlaxoSmithKline. Dr. Paul Baas is an advisor for Pfizer and Merck Sharp Dohme.

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