The relevance of baseline symptom burden in advanced gastroesophageal cancer to treatment toxicity assessment

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Abstract

Advanced gastroesophageal adenocarcinoma (GOA) is a poor prognosis disease associated with significant symptom burden at diagnosis. In this post-hoc analysis of the GO2 trial, we report the baseline symptom burden in the GOA patient cohort. We also demonstrate that by taking pre-treatment symptom burden into consideration, observed treatment related toxicity is significantly lower. We conclude that the reported perceived impact of treatment on toxicity in the GO2 trial was largely driven by baseline disease symptom burden. We propose a need for better methods of reported treatment toxicity in high symptom disease.

Introduction:

The real-world advanced gastroesophageal adenocarcinoma (GOA) population is associated with older age, frailty and significant symptom burden[1]. Evidence guiding management of this population has traditionally come from trials in younger, fitter patients with few co-morbidities, who often do not match the patients seen in clinic[2].

The GO2 randomised clinical trial was established to address this issue by comparing 3 dose levels of Oxaliplatin/Capecitabine chemotherapy (OX)[3] and exploring the impact of each dose on treatment toxicity, quality of life and a novel endpoint overall treatment utility (OTU). Patients of all oesophageal/gastroesophageal junction/gastric cancer histologies were recruited and there was an additional arm of the trial exploring the role of chemotherapy compared to supportive care alone in those in whom there was doubt over whether chemotherapy would be beneficial.

Treatment related toxicity is commonly reported using maximum experienced toxicity, however, this does not take into account the additional burden of multiple toxicities[4]. Additionally, baseline symptoms, which may be misinterpreted as treatment toxicity are not accounted for in this method of reporting; something which may be particularly relevant to a high symptom burden disease such as GOA.

In this article we aimed to explore the baseline symptom burden of the older, frailer GO2 GOA population. We also aimed to explore the impact of this baseline symptom burden on the change in experienced maximum toxicity when compared the that reported in the GO2 trial.

Methods:

This is an analysis of the clinical dataset obtained during the GO2 trial[3]. The GO2 trial (ISRCTN44687907) was an academic, multicentre, open-label randomized trial, approved by the UK National Research Ethics Service, overseen by independent Trial Steering and Data Monitoring & Ethics Committees. All participants gave fully informed written consent. Patients had locally advanced and/or metastatic gastroesophageal cancer that was not pre-treated and were felt to be unsuitable due to advanced age/frailty for full-dose chemotherapy.

Baseline assessments included but were not limited to EORTC QLQ-C30/OG25, EQ-VAS and toxicity assessment using Common Terminology Criteria for Adverse Events (CTCAEv4). Toxicity was also recording before each cycle of chemotherapy and at the end of treatment.

Demographic data was compared using t-test for continuous variables and chi-squared analysis for categorical variable. Toxicity data is reported as a descriptive analysis. P values are 2-sided and considered significant at an overall significance of 5%. R version 4.1 was used for statistical analysis.

Results:

Patient demographics

From the initial 559 patients included in the trial, 464 patients with HER2 negative/unknown GOA were eligible for analysis; 431 in the likely to benefit arm and 33 in the uncertain to benefit arm of the trial. HER2 positive patients were excluded.

Table 1 shows the baseline demographics of the GOA population according to treatment arm. The median age of the population was 77 years old (range 51–91 years), with 60.8% of patients aged 75 years or older. 75.9% of patients were male and 31.9% of patients had a PS of 2 or greater. There was a fairly even distribution according to site of primary tumour. Most of the data relating to prior adjuvant chemotherapy was not recorded, therefore it is difficult to comment on these results.

Median age of the uncertain arm of the trial was higher than the likely to benefit arm (80 vs 76 years), but the difference between groups was not significant. ECOG performance status was the only significantly different baseline demographic, with a greater proportion of PS 2 patients in the uncertain arm. This may reflect a reluctance of clinicians to allocate poorer ECOG PS patients to the likely to benefit arm, based on their previous clinical experience and standard use of ECOG PS as a decision-making tool.

Table 1

Demographics of the HER2 negative, non-squamous population in the GO2 trial. Patients are grouped according to initial stratification to 'likely to benefit' and 'uncertain to benefit' arms. Continuous data was analysed using unpaired t-test, categorical data was analysed using chi-squared analysis.

	Total (N = 464)	Likely to benefit (N = 431)	Uncertain to benefit (N = 33)	P-value
Age (years)				
Median (Min, Max)	77.0	76.0	80.0 (66.0, 87.0)	1
Age group				
< 75	182 (39.2%)	176 (40.8%)	6 (18.2%)	0.037
≥ 75	282 (60.8%)	255 (59.2%)	27 (81.8%)	
ECOG				
0	68 (14.7%)	68 (15.8%)	0 (0%)	< 0.001
1	247 (53.2%)	237 (55.0%)	10 (30.3%)	
2	136 (29.3%)	116 (26.9%)	20 (60.6%)	
> 2	12 (2.6%)	9 (2.1%)	3 (9.1%)	
Sex				
Male	352 (75.9%)	331 (76.8%)	21 (63.6%)	0.235
Female	112 (24.1%)	100 (23.2%)	12 (36.4%)	
Site of Primary				
Oesophagus	153 (33.0%)	138 (32.0%)	15 (45.5%)	0.634
GOJ	116 (25.0%)	110 (25.5%)	6 (18.2%)	
Gastric	193 (41.6%)	181 (42.0%)	12 (36.4%)	
Metastases present				
Present	308 (66.4%)	291 (67.5%)	17 (51.5%)	0.172
Absent	156 (33.6%)	140 (32.5%)	16 (48.5%)	
Dose level				
100% OX	144 (31.0%)	144 (33.4%)	0 (0%)	< 0.001
80% OX	143 (30.8%)	143 (33.2%)	0 (0%)	
60% OX	161 (34.7%)	144 (33.4%)	17 (51.5%)	
BSC	16 (3.4%)	0 (0%)	16 (48.5%)	

	Total (N = 464)	Likely to benefit (N = 431)	Uncertain to benefit (N = 33)	P-value
Prior adjuvant chemotherapy				
Yes	39 (8.4%)	37 (8.6%)	2 (6.1%)	0.305
No	45 (9.7%)	38 (8.8%)	7 (21.2%)	

Baseline symptom burden

The symptom burden in the cohort was striking (Table 2), including symptoms not traditionally associated with GOA or screened for in clinic appointments. 88.1% of patients reported fatigue, 47.2% reported nausea and vomiting, 63.8% reported pain, 50% reported dyspnoea, 53.7% reported insomnia, 70% appetite loss, 54.7% constipation and 19.8% diarrhoea.

Table 2
Baseline symptom burden according to patient reported EORTC QLQ-C30 baseline questionnaire in the HER2 negative, non-squamous population in the GO2 trial. Symptoms were recorded as present or not based on patient responses.

	Certain (N = 429)	Uncertain (N = 35)	Overall (N = 464)	P-value
Fatigue				
No	40 (9.3%)	2 (5.7%)	42 (9.1%)	0.774
Yes	377 (87.9%)	32 (91.4%)	409 (88.1%)	
Missing	12 (2.8%)	1 (2.9%)	13 (2.8%)	
Nausea and Vomiting				
No	218 (50.8%)	18 (51.4%)	236 (50.9%)	0.992
Yes	203 (47.3%)	16 (45.7%)	219 (47.2%)	
Missing	8 (1.9%)	1 (2.9%)	9 (1.9%)	
Pain				
No	148 (34.5%)	11 (31.4%)	159 (34.3%)	0.947
Yes	273 (63.6%)	23 (65.7%)	296 (63.8%)	
Missing	8 (1.9%)	1 (2.9%)	9 (1.9%)	
Dyspnoea				
No	201 (46.9%)	16 (45.7%)	217 (46.8%)	0.988
Yes	214 (49.9%)	18 (51.4%)	232 (50.0%)	
Missing	14 (3.3%)	1 (2.9%)	15 (3.2%)	
Insomnia				
No	186 (43.4%)	16 (45.7%)	202 (43.5%)	0.962
Yes	231 (53.8%)	18 (51.4%)	249 (53.7%)	
Missing	12 (2.8%)	1 (2.9%)	13 (2.8%)	
Appetite loss				
No	117 (27.3%)	8 (22.9%)	125 (26.9%)	0.848
Yes	299 (69.7%)	26 (74.3%)	325 (70.0%)	
Missing	13 (3.0%)	1 (2.9%)	14 (3.0%)	
Constipation				

	Certain (N = 429)	Uncertain (N = 35)	Overall (N = 464)	P-value
No	186 (43.4%)	12 (34.3%)	198 (42.7%)	0.582
Yes	232 (54.1%)	22 (62.9%)	254 (54.7%)	
Missing	11 (2.6%)	1 (2.9%)	12 (2.6%)	
Diarrhoea				
No	332 (77.4%)	27 (77.1%)	359 (77.4%)	1
Yes	85 (19.8%)	7 (20.0%)	92 (19.8%)	
Missing	12 (2.8%)	1 (2.9%)	13 (2.8%)	

Patients in the younger cohort (age < 75) had a higher baseline symptom burden than the older age group across all symptoms, both in presence or absence (data not shown) and in EORTC score (data not shown). This higher symptom burden may partly explain the lower baseline quality of life observed in the younger population (baseline VAS, p = < 0.001) and may also represent a different disease biology.

Exploring the results from the EORTC QLQ-OG25 questionnaire at baseline (Table 3), we can see that there is a significant gastroesophageal specific symptom burden. Two-thirds of patients report difficulty with swallowing solids, with 25.9% and 15.7% having difficulty with soft food and liquids respectively. Stomach pain and discomfort was reported by more than half of patients, while 58% reported discomfort on eating and 34.1% stated they experienced pain on eating. These issues are compounded in the 37.9% who report loss of taste.

Table 3
EORTC QLQ-OG25 symptom burden at baseline in the HER2 negative, non-squamous population in the GO2 trial.

	Certain (N = 429)	Uncertain (N = 35)	Total (N = 464)
Difficulty with solid food			
No	129 (30.1%)	13 (37.1%)	142 (30.6%)
Yes	288 (67.1%)	21 (60.0%)	309 (66.6%)
Missing	12 (2.8%)	1 (2.9%)	13 (2.8%)
Difficulty with soft food			
No	304 (70.9%)	25 (71.4%)	329 (70.9%)
Yes	112 (26.1%)	8 (22.9%)	120 (25.9%)
Missing	13 (3.0%)	2 (5.7%)	15 (3.2%)
Difficulty with liquids			
No	351 (81.8%)	29 (82.9%)	380 (81.9%)
Yes	68 (15.9%)	5 (14.3%)	73 (15.7%)
Missing	10 (2.3%)	1 (2.9%)	11 (2.4%)
Stomach pain			
No	196 (45.7%)	18 (51.4%)	214 (46.1%)
Yes	219 (51.0%)	16 (45.7%)	235 (50.6%)
Missing	14 (3.3%)	1 (2.9%)	15 (3.2%)
Stomach discomfort			
No	150 (35.0%)	13 (37.1%)	163 (35.1%)
Yes	266 (62.0%)	21 (60.0%)	287 (61.9%)
Missing	13 (3.0%)	1 (2.9%)	14 (3.0%)
Discomfort on eating			
No	166 (38.7%)	13 (37.1%)	179 (38.6%)
Yes	249 (58.0%)	20 (57.1%)	269 (58.0%)
Missing	14 (3.3%)	2 (5.7%)	16 (3.4%)
Pain on eating			

	Certain (N = 429)	Uncertain (N = 35)	Total (N = 464)
No	273 (63.6%)	20 (57.1%)	293 (63.1%)
Yes	144 (33.6%)	14 (40.0%)	158 (34.1%)
Missing	12 (2.8%)	1 (2.9%)	13 (2.8%)
Loss of taste			
No	257 (59.9%)	19 (54.3%)	276 (59.5%)
Yes	162 (37.8%)	14 (40.0%)	176 (37.9%)
Missing	10 (2.3%)	2 (5.7%)	12 (2.6%)

Together, with the EORTC QLQ-C30 baseline data, this shows the need for early supportive care measures in this population – not just in those who will go on to have treatment but also in those for whom symptom control is the primary goal.

Impact on toxicity analysis

Using formal toxicity assessment data according to CTCAEv4 at baseline (a representation of disease symptom burden), we explored the impact this had on treatment toxicity reporting, which traditionally uses maximum toxicity experienced. For this analysis we used the 431 patients in the likely to benefit arm.

Table 4
shows the change in maximum toxicity from baseline for haematological and non-haematological toxicity according to CTCAE grading. The data shows that 150 (34.8%) of patients had a deterioration in haematological toxicity and 219 (50.8%) of patients had deterioration in non-haematological parameters. The remaining patients either remained stable or had symptom/parameter improvement.

	Change in maximum CTCAE toxicity from baseline							
	-4	-3	-2	-1	0	1	2	3
Haematological	0	3	10	24	177	105	42	3
Non-haematological	0	3	23	40	146	174	40	5
Overall	0	1	3	12	125	206	76	8

Table 4. Change in maximum CTCAE toxicity from baseline in GOA patients who received palliative chemotherapy in the GO2 trial. Figures represent number of patients.

Overall change in toxicity was calculated by combining the results from haematological and non-haematological toxicities (Table 4). 290 patients (67.3%) experienced an increase in maximum toxicity,

125 (29%) had stable toxicity and 16 (3.7%) had improved maximum overall toxicity. The majority of toxicity deterioration (206 of 290 patients, 71%) is by a single toxicity grading level. Only 8 (1.8%) patients experience what would traditionally be recorded as a grade 3 + toxicity. This is compared to the 209 (48.5%) patients who were recorded as having grade 3 + toxicity if baseline toxicity was not taken account of.

Discussion:

GOA is known to be a high symptom burden disease, but little data exists in the older, frailer population who are typically excluded from trials, but yet are commonly encountered in clinical practice. Early identification of symptoms and implementing targeted interventions has been shown to improve overall survival in GOA[5], therefore knowledge of expected symptom prevalence is essential. Our study utilised the completed GO2 trial to analyse and report the baseline symptom burden in a population 461 patients with GOA.

Overall, we observed that the general symptom burden is high. Importantly this symptom burden includes symptoms that are not typically considered to be associated with GOA, such as dyspnoea and insomnia. Interestingly, although haemoglobin is significantly lower (data not shown) in those with dyspnoea compared to those without, the median values for both male and females are within the normal range, suggesting that haemoglobin level may not be the main driver of this effect. When Pro-BNP is explored as a surrogate for cardiac function, those without dyspnoea had a higher mean level, suggesting cardiac function is also unlikely to be the driver.

We propose that it is the underlying systemic effects of advanced cancer that produces many of the constitutional symptoms a patient experiences and that these contribute to an overall picture of frailty.

The high symptom burden highlights the need for early supportive care measures in this population – not just in those who will go on to have treatment but also in those for whom symptom control is the primary goal.

The second objective of this study was to assess the impact the baseline symptom burden had on reported treatment related toxicity data. If we only consider the toxicity recorded during treatment, it could be concluded that treatment is associated with a significant toxicity burden. However, when we adjust for the presence of baseline symptoms and filter for additional toxicity treatment brings, 1 in 3 patients either experience no change in maximum toxicity or an improvement. Importantly, even in those in whom toxicity deteriorates, the majority are by a single toxicity grade. As such, we propose the impact of treatment on toxicity is significantly lower than previously reported and most of the symptom burden is a result of disease. Defining alternative methods of identifying toxicity that is solely due to treatment is an important research goal as we strive for personalised medicine and shared decision making. This is particularly important for a cohort of patients such as advanced GOA, in whom prognosis is poor.

Conclusion:

Symptom burden in advanced gastroesophageal adenocarcinoma is significant and covers a wide spectrum of symptoms. Baseline symptoms can be subsequently misinterpreted as treatment related toxicity. This could have important implications for toxicity reporting using the traditional methods of maximum experienced toxicity as shown in this dataset.

Declarations

Acknowledgements

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Author contributorship

MAB and RDP developed the concept. MAB drafted the manuscript. All authors approved the final draft.

Ethical approval

This is a post-hoc analysis of the GO2 clinical trial dataset covered under the trial ethics application (ISRCTN44687907).

Consent for publication

N/A

Data availability

Deidentified patient data with data dictionary is available. Researchers approved by the GO2 Trial Management Group can access following approval of a research proposal.

Competing Interests

RDP has undertaken speaking, consulting and advisory roles for Eli Lilly, BMS, Pfizer, Sanofi, Servier; and received research funding (not related to the work in this manuscript) from Astra Zeneca, Roche, MSD, Merck serrano, Eli Lilly, Five Prime Therapeutics, Clovis, Boston Biomedical, and Janssen. MAB has no competing interests to declare.

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