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Unmet clinical needs in the management of advanced melanoma: findings from a survey of oncologists

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Advanced melanoma is a life-threatening cancer with limited life expectancy. The recent introduction of new targeted systemic therapies has provided clinicians with the means to potentially extend survival for the first time. However, the chance of cure remains very low and treatment-induced toxicity is well described. This qualitative study was undertaken to evaluate clinicians' assessment regarding the key concerns in managing advanced melanoma following the introduction of these new treatments. Three hundred and forty-three oncologists were surveyed online between August and November 2012 (in 11 countries) and March and April 2013 (in an additional country). Analysis of free-text responses identified 23 clinical issues of concern across all countries. Of these, the most common clinical concerns were drug toxicity and tolerability, followed by limited treatment effectiveness and limited treatment options. These results suggest that despite the promise of the two new agents in the field, clinicians are still concerned about the limitations of current treatment options, recognising that there remains a significant unmet need in the treatment of advanced melanoma.

Keywords: advanced melanoma, clinical concerns, treatment options, attitudes, international, unmet need.

INTRODUCTION

Advanced (unresectable or metastatic) melanoma is a life-threatening cancer, with an increasing incidence rate (Lens & Dawes 2004). Until recently, non-surgical treatment options relied on conventional cytotoxic chemotherapy without demonstrable overall survival benefit, highlighting the need for new treatments with greater efficacy (Lebbe *et al.* 2012; Bedane *et al.* 2013; Lorigan *et al.* 2014).

The treatment landscape changed significantly with the development and licensing of novel systemic agents for example: ipilimumab and vemurafenib; both products have demonstrated overall survival benefit in patients with advanced melanoma (Hodi *et al.* 2010; Chapman *et al.* 2011; Robert *et al.* 2011). The anti-CTLA4 monoclonal antibody, ipilimumab, was approved by the European Commission in August 2011 for patients with advanced (unresectable or metastatic) melanoma who have received prior systemic therapy, while the BRAF inhibitor, vemurafenib, was approved in February 2012 for the treatment of advanced BRAF V600 mutant melanoma; activating mutations in BRAF occur in 50–60% of

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melanomas (Ravnan & Matalka 2012). Both products have also been approved in Australia, Canada, Brazil and Mexico.

This article provides data from practising clinicians on the impact of the newer agents in the treatment landscape for melanoma to supplement the observational data already in the literature.

The aim of this study was therefore to evaluate clinicians' assessment regarding the key concerns in managing advanced melanoma following the introduction of these new treatments.

METHODS

This study was part of a larger ethics-approved online survey of clinicians, designed to collect information about the current treatment of advanced melanoma in Australia, Belgium, Brazil, Canada, France, Germany, Italy, Mexico, the Netherlands, Spain, Sweden and the UK. The survey was conducted between August and November 2012 in all of the listed countries with the exception of Mexico, where it was conducted between March and April 2013.

The questionnaire used in the survey comprised 63 questions relating to the respondents' clinical practice in the previous 12 months. The final question asked respondents to list the top three issues that most concerned them in the current management of advanced melanoma. The analysis of responses to this question is reported in this article.

Questionnaire development

The questions were developed in collaboration with two physicians who treat advanced melanoma, and were based on questions arising from a literature review; MEDLINE was searched via PubMed using the following search terms alone or in combination "advanced melanoma", "metastatic melanoma", "case review", "treatment patterns", "prescribing patterns" and "guidelines". ESMO and country-specific oncology associations were also searched for treatment guidelines.

The questionnaire was reviewed by one oncologist in each study country to ensure country-specific relevance prior to being translated for the pilot phase of the study.

Pilot phase

Before implementation of the main phase of the study, a pilot phase was carried out involving two clinicians from each country. The purpose was to check the relevance, clarity and usability of the questionnaire.

Sampling lists for each country were provided based on an established panel of clinicians in the oncology field. Other studies using this panel have been published in recent years (Chancellor *et al.* 2011).

Potential participants were contacted by email where the study was explained and informed consent sought. Those wishing to take part were directed to a web-based screener questionnaire to assess their eligibility.

Physicians eligible to participate were board-certified or accredited in their specialty, had at least 2 years' experience in their current role, and had treated at least five patients with AJCC stage III/IV melanoma in the preceding 12 months. Reimbursement was provided to respondents in recognition of time spent completing the survey; this has been shown to improve response rates (Edwards *et al.* 2002).

Two study researchers observed how each pilot participant interacted with the web interface to evaluate the ease of use of the questionnaire. Following completion of the questionnaire, respondents were interviewed by telephone using a structured discussion guide to investigate perceptions of the questionnaire. Minor amendments were made to the questionnaire based on the feedback received.

Main phase

In the main phase between 24 and 30 clinicians from each of the 12 countries completed the questionnaire. A target of 30 responses per country was set; sample size was determined to reflect a balance between covering all major regions and types of treating institution in each country and feasibility of recruitment. The same established panel and recruitment process used in the pilot was used in the main phase.

In Belgium, the Netherlands and Sweden, the target of 30 clinicians was not achievable in the timeframe of the study and the quotas that allowed no more than three respondents from the same hospital or centre was permitted and limited the number of respondents per region. In these countries with a lower population, there are fewer institutions and clinicians treating advanced melanoma.

Data analysis

The data analysis was descriptive to reflect the non-comparative nature of the survey.

Data collected in pilot phase was not included in the final analysis.

Free-text responses from the question regarding issues in current management of melanoma were translated from the local language into English. Although participants

were asked for the top three issues in the current management of melanoma, some included more than three answers, in these cases all responses were included. Duplicate answers were removed. For each country, the responses were coded into categories until saturation. The coding of the data was undertaken by two researchers and then checked in consultation with other project members. After all country data were grouped, the categories were reviewed again to ensure none overlapped, and the final categories were discussed and refined by the project team. Descriptive statistics (means and counts) were then used to summarise the responses by categories; it was considered inappropriate to conduct any further statistical analysis since the responses were free text analysed using qualitative methods and we were interested in trends rather than establishing statistically significant differences between countries.

RESULTS

Three hundred and forty-three clinicians (90% oncologists, 10% dermatologists) participated in this study. The number of institutions represented per country ranged from 14 (Sweden) to 26 (Brazil, Spain). Participants from each country had a mean of between 8 and 16 years' of experience. The mean number of advanced melanoma patients treated in the preceding 12 months was 44.

Most participants had experience with using ipilimumab and vemurafenib (Table 1); in France, Italy and the UK, over 80% of participants had prescribed ipilimumab, vemurafenib or both. Smaller proportions of participants from Brazil and Mexico reported experience with the novel agents: 33% in both countries for vemurafenib and 40% in Brazil and 50% in Mexico for ipilimumab.

Table 1. Participants with experience of using ipilimumab and vemurafenib

Countries	ipilimumab, *n* (%)	vemurafenib, *n* (%)	Participants, *n*
Australia	22 (73)	27 (90)	30
Belgium	23 (96)	17 (71)	24
Brazil	12 (40)	10 (33)	30
Canada	18 (60)	21 (70)	30
France	26 (87)	26 (87)	30
Germany	25 (83)	23 (77)	30
Italy	25 (83)	25 (83)	30
Mexico	15 (50)	10 (33)	30
The Netherlands	23 (88)	19 (73)	26
Spain	19 (63)	21 (70)	30
Sweden	19 (83)	12 (52)	23
UK	29 (97)	27 (90)	30
Overall	256 (75)	238 (69)	343

Clinical concerns in the management of advanced melanoma

For analysis, 998 answers were included, of these, 712 (71%) related to clinical issues, 189 (19%) related to the cost and reimbursement and 97 (10%) related to drug or clinical trial availability. The clinical issues resulted in 23 categories of clinical concern for physicians in the treatment of advanced melanoma (Table 2). Toxicity and tolerability of treatment was the most commonly raised concern. Other common clinical concerns include limited treatment effectiveness and limited treatment options.

Toxicity and tolerability

Toxicity and tolerability of treatment were among the top three issues for all countries, and were raised by just under half of all participants (mean 47%; range from 30% in Spain and Mexico to 64% in Belgium). Similar proportions of the participants from most European countries reported toxicity and tolerability as a concern, including France (57%), the Netherlands (58%), Sweden (57%) and Italy

Table 2. Clinical themes identified as concerns raised by participants

Concern	Mentions, *n*	Participants (%)
Toxicity/tolerability*	162	47
Poor survival	78	23
Limited treatment options*	68	20
Limited treatment effectiveness*	68	20
Low or short response*	60	17
Rapid disease progression	50	14
Drug resistance*	32	9
HRQL	30	9
Biomarkers	28	8
Treatment of (brain) metastases*	27	8
Lack of established treatment algorithm	23	7
Performance status	14	4
Limited treatment options for BRAF wild type	13	4
Clinical guidelines	11	3
Advanced disease at diagnosis	10	3
Age	10	3
Centralising care	8	2
Understanding of disease biology	8	2
Recurrence	4	1
Tumour load	3	1
Mode of administration	2	1
Patient preference	2	1
Patient subgroups	1	<1
Total	712	

*Raised by at least one participant in all countries.

(50%), with higher proportions in Germany (63%) and in Belgium (64%). Half the Canadian participants (50%) also listed toxicity and tolerability as an issue. Rates were a little lower in the UK and Brazil (37%), and Australia (40%). Examples of participants' responses for this category include, 'toxicity of new targeted therapies', 'the toxicities associated with the most effective therapies' and 'toxicity of ipilimumab'.

Limited treatment effectiveness

Common areas of concern related to clinical effectiveness included: poor survival (23% of participants); limited treatment effectiveness (20%); low or short response (17%); rapid disease progression (14%); drug resistance (9%) and treatment of brain metastases (8%) (Table 2).

By country, the proportion of participants citing concerns about effectiveness varied. For example, 37% of respondents from Italy reported limited treatment effectiveness, 32% of respondents from Belgium cited poor survival and 40% of respondents from Germany reported low or short response as concerns with current available treatments. Examples of participants' responses for this category include, 'the treatments' limited efficacy in some patient subgroups' and 'poor effectiveness'.

Limited treatment options

Overall, limited treatment options were the third most commonly cited clinical issue. Approximately, one-third of the participants raised concerns about limited treatment options in Sweden (35%), Canada and the UK (33%), and France (30%), compared with 8% in Italy and the Netherlands. In Mexico and Brazil, where fewer participants had experience of using ipilimumab and vemurafenib (Table 1), 23% and 13% of participants, respectively, cited this issue. Examples of participants' responses for this category include, 'still a lack of many targeted therapies' and 'few therapy options'.

Differences in concerns between countries

The top six concerns in each country were also compared (including top seven or eight for equally ranked issues). As reported above, toxicity and tolerability was reported as a top concern in all countries. Poor survival was one of the top concerns for 10 countries, limited treatment options for eight countries and limited treatment effectiveness for seven countries.

Concerns that were among the top six or seven issues for only one or two countries include: health-related quality of life, e.g. 'try to maintain patients' quality of life' (21% and 17% of participants in Belgium and Spain); biomarkers, e.g. 'the delays of BRAF testing'; 'it is too complicated to do BRAF testing' (Canada, 20%; and Spain, 17%); lack of an established treatment algorithm, e.g. 'the lack of validated treatment flow charts (sequence of drugs)', 'rapidly evolving new drugs but the sequencing of them makes it difficult' (Italy, 13%; and Mexico, 17%); centralising care, 'centralising treatment stage IV melanoma is important for good information, but means high costs for that centre' (the Netherlands, 27%); limited treatment options for BRAF wild type specifically, e.g. 'third-line options in braf wild types', 'first-line therapy for BRAF wild-type patients' (UK, 17%); and treatment of (brain) metastases, e.g. 'brain metastases – epileptic episodes and respiratory crises', 'metastases, especially brain metastases' (Italy, 13%).

Taking the overall top six issues (Table 2) and comparing the proportion of European participants citing them with those in Australia and Canada or Mexico and Brazil, the key areas of difference were toxicity/tolerability and limited treatment effectiveness; these concerns were mentioned by fewer participants in Brazil and Mexico than in Europe or Australia and Canada. Similar proportions of participants highlighted the other concerns in both Europe and the rest of the world (Fig. 1).

DISCUSSION

While some data on prescribing patterns and outcomes can be gathered from chart reviews and registries, these types of studies cannot explore the rationale behind prescribing choices or clinicians' views and priorities regarding management of complex diseases such as melanoma. While surveys are subject to a number of potential sources of bias (e.g. selection and re-call), this survey was designed to try and minimise such biases, and included a large number of participants (343 across 12 countries).

Our findings show that although most participants reported using ipilimumab and vemurafenib, clinicians continue to have concerns about treatment options despite the promise of these new agents. The data show that these concerns centre on toxicity and tolerability, and effectiveness (relating to limited treatment effectiveness, poor survival, and low or short response duration).

Although there are some data on treatment patterns in advanced melanoma, most previous work was conducted before these new agents were released, and is limited to retrospective observational studies rather than investigating the views of clinicians themselves (Lebbe *et al.* 2012; Bedane *et al.* 2013; Lorigan *et al.* 2014). The utility of this

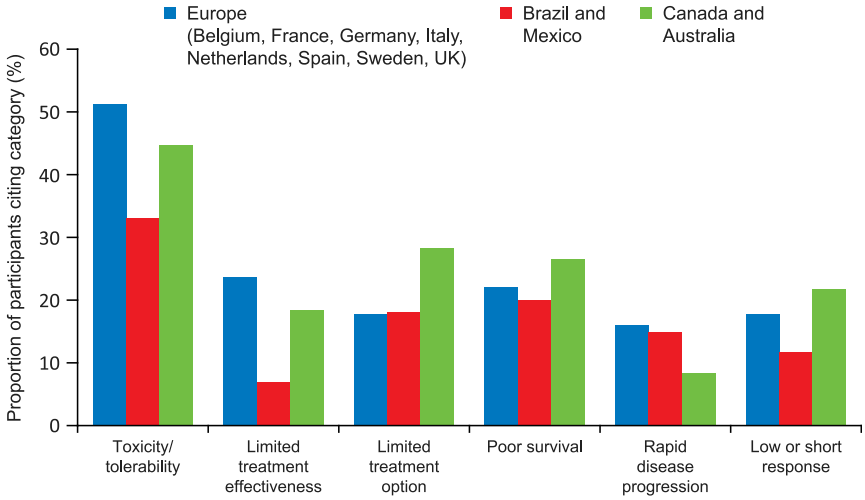

Figure 1. Regional differences in top six concerns raised by clinicians.

study is in providing qualitative data which can add depth to treatment patterns data and further enhance the understanding of clinical practice as it evolves with experience of new agents. Our study highlights that concerns regarding limited treatment options remain after the introduction of ipilimumab and vemurafenib, and that in the world of clinical practice, there are still questions about long-term effectiveness and tolerability and treatments for patients with brain metastases. Furthermore, there were comments from most countries about sequencing of treatment and clinical guidelines indicating that respondents may be looking for more evidence to assist with incorporating novel therapies alongside, or instead of existing agents. We speculate that this was due to respondents' lack of familiarity with therapies targeting the immune system in oncology. Ipilimumab was the first example of immunotherapy in a major tumour, clinical trial data were limited when it first became available, and at the time this survey was conducted, there was no data on the use of ipilimumab prior to or following treatment with vemurafenib. In future, surveys of clinicians, such as this one which allow exploration of key issues and treatment patterns could be used to understand real world practice immediately following the launch of new therapies or new classes of therapy. If the study reported here were repeated today, following the recent introduction of further novel therapies for treatment of melanoma, it would be of interest to see if, and how, clinicians concerns have changed, and the rationale behind their prescribing practice. Ipilimumab and vemurafenib were only licensed a few months before this study was carried out, and health technology assessments of the agents had not been conducted; therefore, the agents were not reimbursed by public health systems in many countries, so it was perhaps surprising that so many participants in the study had experience using these agents. We infer that some participants had gained experience of using the new agents through clinical trials and expanded access programmes.

The results show some regional variations that reflect differences in health care systems and access to drugs, particularly for Brazil, Mexico, Australia and Canada where the availability of treatments and clinical trials was more frequently reported as an issue of concern compared to Europe. It is also clear, however, that although the treatment landscape is evolving, clinicians remain concerned that the number of well-tolerated therapies offering durable response and long-term survival benefit is extremely limited; particularly for patients with BRAF wild-type disease or who cannot tolerate the newly introduced agents.

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