

Short Communication

Therapy Preferences in Melanoma Treatment

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Summary

Within a focus group stakeholders (a melanoma patient, a melanoma patient's relative, a palliative care specialist, an oncologist, a dermatologist, a medical ethics specialist, a surgeon experienced in oncological care and two representatives of the Department of quality management dealing with patient affairs) discussed following a briefing on different melanoma therapy options. Recently approved drugs (ipilimumab), chemotherapy with dacarbazine as well as palliative care medicine were object of discussion regarding survival gains, quality of life and treatment costs.

Further more, a hypothetical situation was discussed within the focus group that should show how intensive the willingness to pay for a few months of prolonged survival is: the patient received the money for the new drug and could either spend it for this new drug or otherwise use it for something else. Since the costs of the new therapy are a large burden on the health system, its advantages have to be weighed against its costs.

Judgment was not straightforward because this new therapy has a low response rate, a high rate of treatment-related adverse events and very high costs. Decision making is influenced by medical factors, experience, health status and social networks. Especially the physicians have still seen possible alternative treatment options in chemotherapy and palliative care.

More research on this topic is needed to fully understand how patients and health care providers value the quality versus the quantity of life and their willingness to pay for it.

Abstract

Background

Recently approved expensive cancer drugs (ipilimumab) may cause marginal life prolongation as well as severe treatment related adverse events. This study aimed to examine melanoma patient's and health care providers attitude towards this new therapy option with regard to preference of quality vs. length of life.

Methods

Within a focus group stakeholders (a melanoma patient, a melanoma

patient's relative, a palliative care specialist, an oncologist, a dermatologist, a medical ethics specialist, a surgeon experienced in oncological care and two representatives of the Department of quality management dealing with patient affairs) discussed following a briefing on a controversial drug that is highly-priced with frequent treatment related adverse events and low objective response rates (ORR) but long-lasting responses (ipilimumab). Discussion was guided by five questions (Supplemental File 1).

Results

There was no general recommendation with regard to using the new drug. However, participants agreed that this drug could not be standard therapy at the current price: the drug itself is highly-priced and health fund incur further cost for the treatment of side effects. Factors considered to influence patient's therapy decisions included previous suffering, current medical condition, lack of alternative treatment options and social networks. There were apparent differences as to acceptable side effects between patient and health care providers, the latter being more critical. Finally, all agreed that investing in prevention measures should and cannot be weighed against spending for treatment of cancer patients and health care provides.

Conclusion

The cost-effectiveness-discussion of new treatments is important since they impose a significant financial burden on society. The

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discourse will lead to a better mutual understanding of patients and thus improve therapy decisions.

Keywords: Benefit; Quality Of Life; Therapy Choices; Cost; Acceptance.

Introduction

Recently new drugs have been approved for the treatment of metastatic melanoma; one of them, ipilimumab, was object of discussion. These drugs show survival benefits [1], yet at costs much higher than previous therapies, i.e. with 120,000 Euros per treatment cycle with ipilimumab, as compared to 10,500 Euros for standard chemotherapy. Ipilimumab shows a median overall survival from 9.1 to 11.2 months in comparison with dacarbazine (DTIC) [1]. However, ipilimumab is associated with frequent immune-related adverse events like colitis, hepatitis, hypothyroidism and objective response rates of about 11%, only [2,3]. Calculating the cost means that the 2.1 months of life time come at a cost of about 109,500 Euros. By contrast, palliative medicine aimed at better symptom control and an improvement of quality of life, on average costs about 4,900 Euros per patient per year [4].

Overall, since objective response rate is low, and the frequency of side effects –part of which is severe- is high it is not easy to make recommendations for an individual patient. Consequently, among physicians a discussion of the value of the therapy to the individual patient has evolved. Furthermore, the cost burden of these high-priced drugs has been viewed critically. If all patients with metastatic melanoma (approximately 1,462 patients at an estimated 5-year prevalence of melanoma of approximately 73,100 patients in Germany [5] and 2.4% of these being classified as stage IV [6] would receive the drug the costs incurred would be 228 million Euros [5,6].

To examine attitudes towards therapy preferences a focus group was conducted. Effectiveness, costs and disadvantages of new therapy options were contrasted with existing therapies regarding survival gains, quality of life and treatment costs.

Methods

A focus group was organized at the Department of Dermatology at the University Hospital of Erlangen. Participants included a melanoma patient, a melanoma patient's relative, a palliative care specialist, an oncologist, a dermatologist, a medical ethics specialist, a surgeon experienced in care of oncological patients and two representatives of the Department of quality management who deal with patient affairs. The discussion was chaired by a private lecturer and senior dermatologist (LH) and documented by the first author (RK). After consent of all participants the discussion was recorded on tape. Beforehand the participants had been briefly informed about the topic, but no preparation was suggested, to leave them unbiased. An information sheet (Supplemental File 1) was designed for the meeting, framing the setting with information on the new drug and containing the questions to discuss. The questions included (i) whether the new drug should be applied as frequently as possible, (ii) which criteria were crucial

for its recommendation, (iii) whether palliative medicine was an alternative, and (iv) whether higher costs were acceptable. With regard to prevention (v) prioritization of resources was discussed as a more cost-effective mean to decrease mortality.

Participants were encouraged to bring forward their opinions and arguments for each topic. After the session the statements were analyzed and described in detail.

Results

Within this focus group session a new therapy option, ipilimumab, was assessed with regard to cost and effectiveness as compared to standard treatment alternatives. Since this therapy has a low objective response rate, a high rate of treatment-related adverse events, please remove double space straightforward. Some quotes are cited in Table 1.

Therapeutic Benefit is Difficult to Translate into Money Values

The main problem raised by the palliative care specialist was a new cost dimension that the pharmaceutical industry had determined for the new drugs. The ethics specialist warned that apart from drug costs, there would be further costs incurred for the treatment of side effects. The palliative care representative calculated that the cost for one patient benefiting from the new therapy would be as high as 1.2 million Euros, when taking an estimated number needed to treat (NNT) of around 10 into account. In comparison the estimated number needed to harm (NNH) would be substantially lower as adverse events are rather common. The ethicist concluded that a cost-effectiveness analysis with respect to DALYs or QALYs would have a poor outcome. The palliative care specialist added that with the 270 billion of the total expenses on health care only 2.2 to 2.5 million people could be treated with drugs in that price range making up only one fortieth of the entire German population. In addition, the dermatologist criticized that the resources spent on ipilimumab as a rather unspecific treatment would no more be available for more specific treatments such as the vaccination with dendritic cells or further research. Finally, however, the ethicist commented that the discussion might be different if the new drug cost less.

Willingness to Pay

Individual value of a therapy vs. value for society

In Germany cancer therapy is covered by the solidary health fund. Within the focus group a hypothetical situation was discussed: the patient received the money for the recently approved therapy and could either spend it for this new drug or otherwise use it for something else. Deciding between these two options should show how intensive the willingness to pay for the drug ipilimumab of each participant is. The patient's relative said that as a patient you would clutch at any straw. Whereas one of the representatives of the Department of quality management said that if she received the money for the innovative therapy and could either use it for paying the therapy or otherwise, she would rather spend it on other things and enjoy as much as possible her remaining life time. In contrast, the ethicist decided he would rather pass the money on to his

daughter. Consequently, having children was discussed as a factor influencing willingness to pay for a longer survival, as the money spent on therapy could as well be handed on to the offspring. The oncologist answered, as he had no children, he would be willing to pay, in case he had a chance for long-term survival.

Since the therapy is covered by the solidary health fund in Germany, one of the quality managers argued it as unfair taking such a big share for oneself. Thereupon her colleague suggested that patients rejecting the highly priced treatment could be rewarded a bonus sum. By all means the main objective should be survival and quality of life for as many patients as possible according to the palliative care provider and all measures should be subordinated to that purpose. There was common consent that treatment for all eligible patients with such high-priced drugs would not be affordable for the German health fund.

One of the quality managers argued that two months saved for the loss in quality of life were not beneficial. Regarding the frequent side effects, the low objective response rate and the on average short survival gain the dermatologist added he would not recommend the therapy to all eligible patients.

Decision-making is influenced by medical factors, experience, health status and social networks.

The medical indication or contraindications were considered as the most important argument for a therapy with ipilimumab, yet the high price also played a role. In the long run, the oncologist regarded the data from studies about long term benefits as decisive.

The patient added that if his medical condition at the moment of decision making was bad he would afford the innovative therapy. However, the oncologist stated that in clinical experience often those patients who encounter severe side effects were less willing to try other treatments with potentially even worse adverse events. Nevertheless, one of the quality managers pointed out that the decision is not made by the patient alone, but also by his family and friends. In accordance with that, the ethicist believed that the patient would be most influenced by his treating physician, as he himself had asked an experienced dermatologist before the meeting if he would recommend the innovative therapy. The patient himself confirmed that he had asked his dermatologist for advice. Therefore, the palliative care specialist suggested seeking advice from three different doctors with regard to the risks of therapy and different risk taking behavior of physicians. As a conclusion, the group agreed on his statement describing the education of the patient about the pros and cons of various therapy options as the essential task for the treating physician as the most important consultant.

Treatment vs. Prevention

It was undisputed that no share of financial resources for melanoma treatment may be spent for prevention instead. All participants of this focus group agreed that the two different concepts therapy and prevention, as well as the individual aspect of the patient and the societal aspect of the general population could not be weighed against each other. Different therapies would be easier to compare and shifts in investment for the one or the other would be politically

defendable. The ethicist agreed that he would have rejected the suggestion to spend a determined share of the treatment resources of the health insurance fund for primary prevention.

Intensive Therapy vs. Palliative Care

For patients refusing any invasive treatment palliative care indeed is an alternative, according to the oncologist. Countering him the palliative care professional proposed to incorporate elements of palliative care early in advanced melanoma treatment, since these concepts were not mutually exclusive. Over the course of the disease there should be a smooth transition between these two approaches. According to him there was a shift from curative or live prolonging attempts to achieving the best possible quality of life for the patient.

Discussion

This is the first report focusing on attitudes towards a new therapy with unprecedented costs, a low objective response rate, a high rate of treatment related adverse events and a prolongation of the median overall survival. Because physicians are often strained to adequately advise patients and furthermore scarce resources of the health fund have to be allocated, it is important to discuss the value of such new treatment options and the willingness to pay for them. Since this therapy is approved in Germany, each patient can receive the therapy. As the health fund covers these costs, this is a substantial cost burden for the health system. Furthermore, different physicians value the gain of the therapy differently according to their risk-taking behavior. Thus, we explored physicians and patient's attitudes towards costs and effectiveness.

Slevin et al. had investigated attitudes of cancer patients, physicians, oncology nurses and healthy controls without any relation to cancer or a medical profession towards two hypothetical chemotherapies with mild and severe adverse events, respectively. The study showed that cancer patients were willing to accept an aggressive treatment with a marginal chance of cure, a longer life or relief of symptoms [7]. This tendency could also be observed during the presented focus group discussion, when healthy people suggested making the most of their remaining life time instead of enduring an aggressive little promising therapy, whereas the patient and his relative preferred even a minimal chance of prolonged survival. The patient's preference for the intensive treatment instead of palliative care in a bad health state was in line with Stiggelbout's findings that patients would rather trade off quality of life for a longer survival [8].

Therapy decisions were claimed to be influenced by various factors including experience, medical condition and personal network. Stiggelbout et al. found that usually people with children would prefer a life prolongation to other treatments [8]. Yet, in the discussion a father rejected the life prolonging therapy due to its costs. He would rather pass the money on to his daughter.

Not only the physician's advice, but also that of the patient's relatives was considered an important factor. Regarding the high probability of severe treatment-related adverse events, one quality manager assumed patients might be prepared to renounce on the expensive therapy, for their quality of life's sake. As an appeal to save costs

for the health fund the suggestion was made to give patients who reject the highly priced treatment a certain extra dividend from the health insurance which is freely available for them. This is similar to the study carried out by Touloukian et al, [9]. In this study cancer patients could choose between two differently effective and priced antiemetics. If they chose the less effective antiemetic they were given a share of 50% of the savings, but in the case of inefficacy could switch to the other one at any time. The majority chose the cheaper drug (58.3% vs. 41.6%) independently of previous cancer conditions or chemotherapy thus saving 28.4% of the costs (\$220,780) [9].

Despite the high rates of adverse events and low objective response rates, the potential of prolonging survival was considered as a chance that patients should not be deprived of. If chemotherapy and other therapy schemes had been tried without success, new costly drugs should be used, if indicated, before the complete transition to palliative care. However, Yun et al. showed that 70.6% of terminally ill cancer patients preferred palliative care to intensive care being aware of their prognosis [10]. Also experts, as in the discussion, tend to recommend palliative care ever earlier in the course of a life-threatening disease, since it eases suffering for patients and their families [11]. Moreover Leung et al. discovered that even if the state of health of final stage cancer patients decreased, their quality of life was still improving until their last day in a palliative care unit [12].

Primary and secondary prevention is able to reduce melanoma incidence and mortality [13, 14]. But although e.g. the Australian primary skin cancer prevention program averted 28,000 disability-

adjusted life-years (DALYs) equal 22,000 life-years saved in Victoria since 1988, all the stakeholders in this focus group unanimously were not prepared to invest a share of therapy resources in primary prevention [15]. Even data on skin screening from Germany could assess an annual decrease of mortality rates by 7.5% for men and 7.1% for women from 2000 to 2009 [16]. In our study spending money for prevention should not lead to any restriction of resources for melanoma therapies according to the participants of the focus group, since the benefit of the general population could not be weighed against the individual benefit.

Although only one focus group on this topic was conducted, the presented results can help to develop further steps to study this important and innovative subject in a questionnaire-based survey on the payoff between quality of life and length of life. Despite of its mere descriptive character the focus group was an essential contribution, since it brought different stakeholders together, in particular patients and physicians.

Conclusion

Since the new therapy are a large financial burden on the health system, its advantages have to be weighed against its costs. The discussion showed that there are very different perspectives on therapies and decision-making for treatment options among patients, patient's relatives, physicians and other health care personnel. This focus group was basis for a subsequent questionnaire-based survey on the payoff between quality of life and length of life [17]. More research on the topic is needed to fully understand how patients, doctors and healthy people value the quality vs. the quantity of life and their willingness to pay for it.

Table 1: Statements from the focus group

Patient's perspective	Physician's perspective
	"I would not apply the new drug A, since success can only be achieved for few patients and costs and side effects are not worth it."
	"The new drug A would always have to be applied if there is no contraindication, due to its approval for stage IV melanoma."
"If I had to decide for a therapy with low objective response rates but high rates of side effects, the advice of my treating physician would influence me the most."	"In therapy decisions concerning treatments with low objective response rates but high rates of side effects, the advice of family and friends is decisive."
"If I was in a bad medical condition I would be willing to take the chance with drug A."	"If the new drug A was cheaper, I would be more willing to take the risk and prescribe the therapy more often."
"I would agree to early palliative care."	"I would rather recommend an early palliative care concept, where emphasis lies on quality of life."
"If there was no chance for healing, I would decide for palliative care."	"Since in the final stages of a cancer disease there is no curative therapy, I would try to emphasize the quality of life for the patient during treatment."
"If I had to pay the sum for the treatment myself and I had it at my disposal I would rather hand the money on (e.g. for the children)."	"I would apply the new drug A restrictively, as otherwise precious resources are lost that could be used for experimental therapies and research."
"If I had to pay the sum for the treatment myself and I had it at my disposal I would rather spend the money in order to afford me something (e.g. a cruise, invite family and friends)."	"I would apply the new drug A restrictively, since it has frequent side effects and only few patients have a benefit."

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We thank all participants of the focus group.

Supplemental File 1:

Work sheet for briefing and structuring the discussion along the five questions raising different topics

Ipilimumab is a new drug (A) for the treatment of advanced melanoma, a human antibody that disinhibits immune defense against cancer cells. It allows for a prolonged survival of 11 months compared to 9 months achieved with conventional chemotherapy with dacarbazine without improving quality of life. In about 60% of the cases autoimmune-mediated adverse events occur. These include endocrinological symptoms, dermatitis, diarrhea and abdominal pain, nausea. The objective response rate of 11% is higher than that of the standard chemotherapy dacarbazine (objective response rate about 5.5 %), yet taken as a whole it is still relatively low. Additionally, the price of approximately 120,000 € per cycle is relatively high in comparison to 10,500 € per cycle for dacarbazine.

In Germany, all the costs for the therapy are covered by the health fund. Yet, since the financial resources are limited, it is questionable that in the future all patients can be treated with such expensive drugs. Physicians increasingly get into the role to attempt to distribute the marginally superior therapies medically and economically meaningful, which proves to be extremely difficult. Additionally, it is not easy to advise a patient a non-curative therapy with a low objective response rate but a high potential for side effects.

New care programs such as palliative medicine aim at an improvement of quality of life at the end of life without wanting to prolong it at any cost, focusing on the freedom from pain and symptoms, as well as psychosocial and emotional well-being. Here costs of approximately 4,900 € per patient cared for per year are incurred. Palliative medical care achieves a better symptom control and an improvement of quality of life.

1. Would you try to apply ipilimumab (A) as frequently as possible or would you prefer different treatment options?
2. Which criteria would be most important for the recommendation of ipilimumab (A) for a patient?
3. Do you consider palliative medicine as an appropriate alternative in the face of a better quality of life instead of a life prolongation?
4. Would you generally be prepared to pay 120,000 Euros for a two months longer survival, if you could alternatively have a palliative medical care according to requirements in an ambulatory or an inpatient setting for 4,900 Euros per year?

Skin cancer can be detected in time by the means of a periodic skin screening and in some cases it can be prevented altogether. The skin screening which is conducted every two years from the age of 35 years with a visual inspection of the whole skin and a purposeful inquiry of the patient costs 16 € per person. For the cost of one

cycle of ipilimumab there can be carried out 7,500 skin screenings and it can be assumed that thereby 28 melanoma are detected at all or earlier and thus the mortality is reduced. Primary prevention by the means of education and structural interventions (e.g. solar panels in schoolyards) in Australia could already demonstrate a decrease in melanoma incidence in the younger population groups. At the same time savings of AU\$2.30 per AU\$1 invested and 28,000 DALYs saved from 1988 until 2009 or alternatively 22,000 life years saved have been calculated.

5. Do you think it would be ethically justifiable if on a political level it were decided that a determined share of the treatment resources (e.g. 10%) of the health insurance fund or a separately charged fee should be invested in primary prevention e.g. in terms of education campaigns or in secondary prevention such as the skin screening, since thus as well the incidence as the mortality can be reduced?

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