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Curation vs. palliation: an attempt to clarify terms¹

Executive Summary

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Executive summary

Introduction

Medical consultations on the aspect of benefit and harm of possible treatment options often refer to research results of clinical studies (particularly randomized controlled trials [RCTs]). They are therefore a key basis for open patient-physician communication in a patient-oriented, participative decision making process. This particularly applies to the treatment of patients with an incurable, advanced and terminal disease. Most advanced cancers, particularly metastatic diseases, can be regarded and used as paradigmatic for this situation.

Research question

The aim of the project reported here was to investigate whether publications of RCTs on patients with advanced cancer take into account aspects of the end of life, the corresponding terminology and the relevance of palliative care needs of these patients.

Based on the publications of treatment studies, the specific aims were to investigate if

- the phase of the disease (progressive terminal disease) was specified correctly (subgoal 1)
- the superior patient-relevant treatment goal (prolongation of life expectancy, improvement of quality of life/best possible maintenance of quality of life or symptom control) was specifically named (the superior treatment goal must not be confused with the study outcomes, but describes the overall goal for the patient that the intervention is clinically intended or hoped to achieve, subgoal 2)
- patient-relevant outcomes (outcomes on overall survival and/or patient-reported outcomes [PROs]) were assessed under particular consideration of the superior treatment goals identified in subgoal 2 (subgoal 3)
- terms such as curation, palliation, palliative medicine/palliative care, best supportive care, supportive therapy and palliative therapy were used and how they were defined (subgoal 4)
- a critical reflection of the benefit-harm profile was conducted (subgoal 5)

Methods

The present systematic review considers publications of RCTs, which investigated the use of disease-modifying treatments (chemotherapy, radiotherapy, surgical or targeted cancer treatment approaches) in adult patients. Studies were to be included that investigated treatments in patients with a median survival time of 24 months maximum. In order to encompass diseases that differ in primary therapies (e.g. chemotherapy, radiotherapy or (neuro)surgical resection), 4 exemplary tumour entities were included. These included studies on glioblastoma (including anaplastic astrocytomas [AA]), lung cancer (stage \geq IIIb), malignant melanoma (stage IV) or pancreatic cancer. Exclusively primary publications of RCTs published in English in selected high-ranked journals, which were identified in a

preliminary search, were considered for the analysis. The systematic literature search was conducted on 14 November 2012 in MEDLINE (Ovid) for the publication period 2003 to 2012 (glioblastoma, malignant melanoma, pancreatic cancer) and 2010 to 2012 (lung cancer). Information from the bibliographic literature search was assessed by 2 reviewers independently of each other in a title and abstract screening for their relevance according to the inclusion criteria. If the relevance was not clear from the title or abstract, the reviewers used the full text for the assessment. If discrepancies occurred, these were resolved by discussion between the 2 reviewers. From all relevant publications, the 25 most recent ones on each disease (according to the publication date) were included in the analysis. This explains the different search periods. The available information, according to the 5 subgoals, was retrieved from the full texts of these 100 publications, transferred to extraction tables, and checked by 2 reviewers.

Results

Subgoal 1

Overall, in 71 of the 100 publications, clear information on the advanced phase of the disease of the patients investigated was provided in the introduction. Publications of studies on patients with pancreatic cancer (n = 21 of 25) most commonly described the phase of the disease clearly, whereas information on this aspect was most often missing in studies on lung cancer patients (n = 8 of 25).

Subgoal 2

In the introduction of 38 publications, prolongation of life, improvement or maintenance of quality of life or symptom control were mentioned as superior treatment goal of the experimental intervention. The number of publications, in which such a treatment goal was mentioned, differed considerably between the 4 diseases: from 13 studies on pancreatic cancer patients to only 3 studies on patients with malignant melanoma. Prolongation of life alone consistently was the most frequently mentioned patient-relevant treatment goal, encompassing 30 cases. Both prolongation of life expectancy and improvement/maintenance of quality of life or symptom control of the patients were mentioned as superior treatment goals in 6 studies. Solely the improvement of quality of life and solely symptom control were identified as the superior treatment goal in 2 publications.

Subgoal 3

Outcomes on overall survival and surrogate outcomes (including combined outcomes like progression-free survival) were the most commonly used primary study outcomes (53 and 45 publications). Safety- or study-specific outcomes were used as primary study outcomes in 3 publications respectively. A PRO was used in no study as primary outcome. Six studies defined more than one primary outcome, and one study explicitly defined no primary outcome. This is why the number of primary outcomes deviates from the number of studies included.

Overall survival was considered as one of the defined study outcomes in 98 of the 100 publications. The exceptions were one study on patients with glioblastoma and one study on patients with malignant melanoma.

In a total of 36 publications, PROs were cited as secondary or tertiary study outcomes in the methods section. In 32 (84.2%) of these cases, the instruments used were specified, and in 31 (86%) cases the corresponding results were also reported in the primary publication at the same time. (Health-related) quality of life was explicitly mentioned in 21 of these 31 studies and was the most common assessed PRO.

In most cases there was consistency of the treatment goals specified according to subgoal 2 and the study outcomes used. In all 30 publications, in which prolongation of life expectancy was identified as superior treatment goal according to subgoal 2, an outcome on overall survival was also defined, in 27 cases as primary outcome. In all publications, in which improvement/maintenance of quality of life or symptom control were named as superior treatment goal besides prolongation of life expectancy, (health-related) quality of life or (other) PROs were also recorded as secondary study outcome besides a primary outcome on overall survival.

Subgoal 4

The terms investigated were used at different frequencies. *Palliative care* was used in only 3 publications, and, like the related terms *palliation* and *palliative therapy*, was not defined. This was similar for the term *curative* and related terms, which were defined rarely and inconsistently. The terms *end-of-life*, *terminal* or *advance care* did not occur at all. By comparison, *best supportive care* was mentioned more often. This term was frequently reduced to drug interventions. Established minimum standards (e.g. regular symptom assessment) were rarely considered.

Particularly the meaning of the term “salvage therapy” was not clear. In most cases it could be deduced from the textual context in the publications that the authors referred to disease-modifying interventions (mostly chemotherapies). The target group for these therapies were patients in a very advanced stage of disease, mostly with recurrence and in whom no further (chemo)therapy was indicated outside of the study setting. The intended treatment goal remained unclear, however. Some authors explicitly addressed the uncertain benefit with regards to the patients’ prolongation of life expectancy despite proven toxicity. This contradicts, to a certain extent, the meaning of the word *salvage*.

Subgoal 5

Both the benefit and the harm side of the interventions investigated were reflected in the discussion in 88 of the 100 publications. The impact of adverse events of the interventions on the patients was reflected adequately in 22 publications. In contrast, the profile of adverse events was played down by using certain phrases in 53 publications.

A conclusion was drawn by authors of all 100 publications. The authors suggested superiority of the experimental intervention in 34 studies, and inferiority in 39 studies. The authors assessed experimental and control interventions to be equivalent in 3 cases, and further investigations were recommended in 24 publications. In 48 of the 100 publications, the authors' conclusions on the benefit-harm profile and/or the conclusion drawn were comprehensible on the basis of the information reported. However, these were not comprehensible in 28 publications, and only partly comprehensible in 17 publications. The authors' conclusions could not be assessed for 7 studies due to missing data or a lack of transparency of the data.

Summary and conclusion

The main goal of the present project to clarify the terms from the context of curation and palliation could not be fully reached because of the inconsistent use and rare definition of terms in the publications investigated.

In approximately half of the studies, overall survival and surrogate outcomes, particularly progression-free survival, were used as the primary outcome. In no case PROs were used as the primary outcome. Irrespective of this, the results on symptoms and particularly quality of life were only reported in 31%.

Whereas as many as 71% of the studies included provided appropriate introductory information on the patients' phase of disease in the publications, a superior patient-relevant treatment goal was only mentioned in approximately 40%. In the vast majority of cases, this was seen in the prolongation of life expectancy, and correspondingly rarely in the improvement of PROs (particularly quality of life). In the publications providing a superior patient-relevant treatment goal, there was good accordance of these goals with the respective (primary) outcomes assessed. By contrast, in the remaining studies, the focus was on a surrogate outcome such as "progression-free survival" or measures of "tumour response" or "tumour control".

In most publications, a balancing of benefit and harm was available in the discussion section, and recommendations for the appraisal of the experimental intervention could be found in all publications. However, these recommendations were only comprehensible primarily in about half the cases in light of the data published.

The following conclusion is drawn from the results:

Key terms in the field of curation and palliation (e.g. curative, supportive and palliative therapy) require terminological clarification and greater precision among the different disciplines. The superior treatment goals of the interventions investigated in the studies should be clearly mentioned in the development of the study protocol and in the subsequent publication. This will facilitate the reflection of the relevance of the study outcomes with regards to this treatment goal. Furthermore, the regular assessment of PROs, i.e. symptoms and quality of life, and the reporting of the corresponding results already in the primary

publications are desirable because of their relevance for the balancing of benefits and harms. Moreover, it should be critically checked whether the terms “tumour control” or “salvage therapy”, but also “progression-free survival”, which are frequently used in publications and concepts, suggest treatment goals which, realistically, are out of reach.

Keywords: palliative care, glioblastoma, lung neoplasms, melanoma, pancreatic neoplasms, randomized controlled trials as topic

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