BRIEF REPORT

IMPROVING THE QUALITY OF THERAPEUTIC REPORTS OF SINGLE CASES AND CASE SERIES IN ONCOLOGY–CRITERIA AND CHECKLIST

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Single cases, case series and retrospective reviews are usually the only possibility for physicians and therapists to conduct their own clinical research, to communicate their therapeutic experiences to the medical community and thus contribute to the body of scientific knowledge. Reports of single cases and case series can preserve and disseminate the knowledge of successful, ingenious and passionate therapists, which has been the main source for dramatic progress of clinical innovations and effective therapies in medical history.[2] At their best, high quality reports of single cases and case series represent the art of cultivating therapeutic experiences and clinical judgment. Although single cases and case series are graded low in evidence-based medicine (and often not considered at all), even in conventional medicine spectacular and well-presented case series, eg, on tumor remissions following an experimental therapy can arouse tremendous public attention.[1] In alternative medicine, especially in the treatment of cancer patients, common scientific communications are reports of single cases, case series and retrospective reviews of the patients of a particular practice, clinic, or hospital. Randomized trials, on the other hand, are expensive, difficult to conduct and do not necessarily reflect daily practice. Moreover, conducting a randomized trial is beyond the scope of the individual alternative practitioner and usually remains the domain of academic institutions and commercial sponsors.

Case reports and case series sometimes appear to present major therapeutic successes—but are often incomplete, vague, and unconvincing and therefore have little chance of being accepted by the medical and scientific community. This could have been different, because usually most of the information missing in the report will be available to the authors and could easily have been presented—or been presented more clearly, but was probably simply overlooked. In the case of oncology, these deficiencies can be crucial: Since spontaneous remission of most cancer forms is very rare, an adequately presented case report or a small case series of tumor remission or even long-standing tumor standstill following an alternative therapy regimen in the absence of conventional cancer therapy indicates a possible therapeutic effect, warranting further investigation. An inadequately presented case report is much easier to discard, thus a potentially effective therapy may be neglected.

There is a simple reason for quality deficiencies of single case or case series reports: While quality criteria for reporting other forms of research—in particular randomized trials—have often been published in detail, quality criteria for the valid reporting of single cases and case series are rare, hard to find and often incomplete themselves. So, what are the characteristics of a well-described single case?

To aid the reporting of single cases and case series in oncology, this paper presents criteria and a checklist. These are based on recommendations of the Office of Cancer Complementary and Alternative Medicine (National Cancer Institute)[3] for preparations of Best Case Series, on common standards for evaluating oncological treatments, eg[4-6] and on the principles of Cognition-based Medicine, which is a scientific method of therapeutic causality assessment, extending contemporary single case methodology by Gestalt recognition.[7,8]

Not all of the items on the checklist will be available in every reported case. Nevertheless, if single case or case series are reported with the intention to suggest or demonstrate the clinical effectiveness of a therapy, the data should be as com-

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plete as possible. Optimally, if relevant data are missing, this should be stated and the possible impact of the missing items on the effectiveness judgment should be discussed. In addition to the checklist items, each author is free to include other information he or she feels is important, eg, anthropological, physiological, therapeutic, biographical or spiritual aspects. However, the inclusion of supplementary data should not lead to the exclusion of essential items. In addition to completeness of data, the author of a case report should always aim at a clear and comprehensible presentation.

If possible, the following information should be included in a therapeutic oncological single case report and summarized in a case series (see also checklist, Table 1):

1. Context and goal

Introductory note, why the case is presented.

2. Diagnosis, stage and site of metastases

Diagnosis, stage, site of metastases, histology, grading, receptor status, genetic or tumor markers if applicable, relevant laboratory findings, date of primary diagnosis, date of diagnosis of recurrence or metastases.

3. Confirmation of diagnosis

The cancer diagnosis has to be confirmed through the examination of tumor tissue by a pathologist. Since a variety of conditions can mimic a malignant process (infections, inflammation, other benign diseases), obtaining tumor tissue for initial diagnosis is mandatory and histological verification of recurrences or at least one metastasis is highly desirable. Additionally, the prognosis and the responsiveness to therapy highly depend on the histological type of cancer.

4. General medical condition

Age, sex, general medical condition, other significant previous or concurrent diseases, smoking history, pre/post menopausal, family history of cancer, other important risk factors for malignant disease, participation in a clinical trial should be mentioned.

5. Main treatment

The treatment assumed to have caused the anti-tumor response or another important improvement of the patient's condition, should be described clearly and detailed: specification of therapy (eg, drug, art therapy, etc.), dosage, mode and frequency of application, change in dosage and application, date of start, end, interruption and modification, etc. This applies both to pharmacologic and to non-pharmacologic treatments.

6. Tolerability and any side effects of the treatment should be mentioned

7. "Hard" endpoint, tumor response

Usually, survival advantage cannot be shown in a single case. Although cancer statistics provide an estimate of median or mean survival of patient groups with the same type of cancer and stage, inter-individual variation is large; thus treatment-associated effects on survival are usually difficult to assess in a single case. Therefore, other endpoints have to be documented. The most reliable endpoint is a reduction in tumor size. Tumor measurements should be done before treatment, during and after completion of treatment, by x-ray, computerized tomography (CT), nuclear magnetic resonance (NMR) tomography, ultrasound, or, if appropriate, by photography. Tumor responses are classified according to the WHO definition[9] into four categories: complete remission (CR), partial remission (PR), no change (NC) and progression (PD). For tumor response each tumor site should be considered and recorded separately. (If disease is not measurable, like lymphangitic lung metastases or skin involvement, the extent of remission has to be estimated). An objective response is considered a tumor reduction of at least 50% (of the area, cross product of the diameter). The person assessing the tumor outcome should be named. Confirmation of tumor response by a second person is desirable. Additionally, time to progression should be documented, as well as total duration of follow-up and the course of disease observed during this follow-up period. In the event of a fatal outcome, the date and cause of death, as well as the results of autopsy should be included.

If the therapy did not aim at affecting tumor growth, but was given to treat other aspects of the patient's condition, eg, side effects of conventional therapies, this should be stated and appropriate endpoints presented. Nevertheless, tumor behavior should be reported.

8. Other Outcomes

Laboratory findings, tumor markers, general medical condition, health status, functional capacity, pain, weight, appetite, vegetative or chrono-biologic findings, mental and spiritual developments, etc., are usually not regarded as sufficient evidence of therapeutic effectiveness. Nevertheless, these domains are often very relevant for the individual patient and therefore should be described. Although validated questionnaires exist for clinical trials, most of them are not suitable for routine use. If changes within these domains have occurred, they should be described clearly and comprehensibly. Concrete descriptions of the magnitude of any change, like the transition from being bedridden to being able to walk 200 meters twice daily are helpful. Work status: full-time, part-time or sick leave from work should be included. Often the improvements in alternative therapies will be within domains of health status or functional capacity, therefore a precise description of each relevant item is essential, including the status before treatment was started, during and after termination of the treatment. The person who assessed these changes (physician or patient) should be noted, also whether an additional independent confirmation of the changes (eg, by a family member, a nurse or a second physician) is available.

9. Temporal relationship between applied therapy and observed outcome

The chronology of the main therapy (No. 5), the chronology of all relevant observed changes in the patient (No. 7 and No. 8) as well as their temporal relationship have to be described precisely for the whole observation period. Often, a graphic presentation, a flow chart or a table will be helpful for the reader.

10. Concomitant therapies

All concomitant therapies—conventional, alternative, pharmacological, non-pharmacological, dietary, vitamins, etc.—should be reported, as well as their duration. This is absolutely essential for therapies that could possibly have had an effect on tumor growth or on the patient's general health. An explicit statement about any concomitant treatments during the 3 months preceding the reported therapeutic intervention (No. 5) should be included.

11. Specific cancer treatments

All concomitant and all preceding cancer treatments—surgery, radiation, chemotherapy, hormones, immune therapies, bone marrow transplants—have to be reported, together with date of application. An explicit statement about any cancer treatments during the 3 months preceding the reported therapeutic intervention (No. 5) should be included, eg, radiation therapy or immune therapy can induce tumor responses with weeks or months delay. If available, tumor response from previous cancer treatments may be reported, as well as a specification of the treatment and the dosage applied.

12. Written consent of the patient regarding the publication of his or her (anonymous) case report should be obtained

13. Criteria of Cognition-based Medicine

(The inclusion of these items is optional. However, if the author believes the reported therapy was effective, these items may strengthen the author's conclusion.) The author should ask himself, whether he thinks the treatment reported was effective for this patient or not, and how certain he is concerning this judgement. If he is certain that the treatment was effective, he should carefully and critically reflect upon what actually convinced him and why he is sure about it. The result of this consideration—the basis of his experience of evidence—should be described and included in the case report. Doing this, the following criteria of Cognition-based Medicine[7,8] may be of help:

- Estimation of the natural history of the disease; how often do spontaneous remissions or spontaneous fluctuations occur?
- How successful were previous treatments?
- How long was the disease present before the reported treatment began?
- Did disease symptoms or signs fluctuate significantly before starting the reported treatment?
- What is the time interval between start of therapy and the first observable improvement of symptoms or signs?
- Was an interruption of the treatment associated with transient disease aggravation?
- Was there any observable temporal relationship between changes in the patient and changes in the treatment dosage or mode of application? If yes, how often and at what intervals was such a relationship observed?
- Were there any particular alterations at the tumor site during therapy, eg, redness, inflammation, altered sensations?
- Was there a local correspondence between treatment application and therapeutic success (eg, the treatment was applied locally and the tumor remitted exclusively or primarily in the corresponding area)?
- Was the treatment applied in a sequence of different interventions and were there particular responses corresponding to each step in this sequence?
- Did complex changes occur in a temporal sequence indicating a therapeutic process? An example: "Four hours after starting therapy fever occurred, after 24 hours the patient experienced altered sensations at the tumor site, after three days a previous chaotic diurnal variation of body temperature suddenly was superceded by a clear diurnal rhythm which remained stable for the following six months, after one week the patient's general condition improved, after four weeks a tumor response was diagnosed."
- Was there a surprising and unexpected positive change of the course of disease?
- What other explanations can be found for the improvement?

CASE SERIES

If several cases are described, the information listed above should be presented for each case (see Table 1 and checklist 1-13). While cohort studies usually present all information statistically, an essential element of case series is the individual information on each patient, although some information can be condensed into a table with each patient represented in a row or column. Depending on the number of patients and the main topic addressed by the article, information of secondary importance in a case series can be described with summary statistics.

If more than one patient is described or referred to in the publication, or if any generalization concerning diagnosis or treatment is made, the total (!) number of patients treated with the particular therapy should be reported. If not available, this number should be estimated. In preparing a case series it is essential to avoid a biased selection of patients (eg, reporting only successful cases and excluding all failures). Optimally, the selection process will be illustrated by a flow diagram demonstrating: (a) how many patients with the diagnosis in question were seen or treated by the authors, (b) how many patients were recommended or referred to the complementary therapy, (c) how many patients actually received the therapy, (d) how

many patients were followed up by the reporting institution, and (e) how many patients are actually presented in the case series. The reasons why some patients are not included in the case series should be mentioned. If important characteristics of excluded patients are known, especially regarding the intervention and outcome, they should be reported. If precise information on the patient selection process is not available, at least an estimate should be provided.

Finally, it should be mentioned if the case series was compiled retrospectively or documented prospectively.

CONCLUSION

Case reports and case series constitute an indispensable part of the scientific literature on cancer therapy. Preparing and presenting good case reports and case series of complementary cancer therapies will usually be worth the effort. Physicians treating cancer patients sometimes make important observations with potential relevance for the medical community, where the appropriate form of presentation would be a case report or a case series. In fact, the literature on complementary cancer therapy is abundant with case reports. However, important information is usually missing in this literature.

Since reports on single cases or case series may have consequences for treatments of other patients, these publications are an issue of high responsibility. Comprehensiveness, relia-

TABLE 1 Checklist as a help for preparing oncological single cases and case series

❒ ✓ **Diagnosis**
❒ Histology, grading, receptor
❒ Stage (at diagnosis and at present)
❒ Site of tumor and metastases
❒ Tumor marker
❒ Laboratory tests
❒ Date of primary diagnosis, of recurrence and metastases

❒ ✓ **Histological confirmation**
❒ Primary diagnosis
❒ Recurrence
❒ Metastases

❒ ✓ **Baseline information**
❒ Age, sex, pre-post menopausal
❒ General medical condition and performance status
❒ Smoking history, family history of cancer, other important risk factors
❒ Relevant medical information

❒ ✓ **Treatment**
❒ Specification of treatment
❒ Dosage
❒ Mode and frequency of application
❒ Start, end, interruption, modification of dosage or application
❒ Tolerability, side effects

❒ ✓ **Tumor response**
❒ Remission according to WHO
❒ How was it assessed?
❒ For CR and PR: all tumor sites considered?
❒ Confirmation by a second person
❒ Time to progression
❒ Duration of follow up
❒ Life-span, date and cause of death

❒ ✓ **Other outcomes**
❒ Laboratory tests
❒ General condition, performance and functional status, others
❒ Weight, appetite
❒ Vegetative state, chronobiology
❒ Quality of life, well being, mental, spiritual aspects
❒ How was it assessed?
❒ Confirmation by a second person?

❒ ✓ **Temporal correspondence between treatment (start, end, interruption) and change of outcome**
❒ Clear, detailed description, easy to follow
❒ All details unequivocally presented
❒ Flow chart, table

❒ ✓ **Concomitant therapies**
❒ Report all concomitant therapies
❒ Duration of application
❒ Therapies during last 3 months
❒ Ask the patient

❒ ✓ **All conventional cancer treatments**
❒ Cancer surgery
❒ Chemotherapy
❒ Hormone therapy
❒ Immune therapy
❒ Radiotherapy
❒ Bone marrow transplant
❒ What? When? How long?
❒ Where? How much? Effect?
❒ Treatment during last 3 months

❒ ✓ **Cognition-based Medicine**
❒ Did my therapy help?
❒ How certain am I?
❒ Why do I think that my therapy was helpful (see criteria pt. 13)?

❒ ✓ **Written consent of patient (or relative)**

❒ ✓ **Addition for Case series (n > 1):**
❒ Number of all (!) patients with the particular diagnosis or treatment (Flow-diagram for selection process)
❒ Characterize excluded patients

❒ ✓ Author
❒ Name, position
❒ **Date of report**

bility and transparency of the information presented are a must. Improving the quality of case reporting is important for physicians and patients.

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