The Reporting of Adverse Events and Deaths Used For Economic Model Inputs Is Inconsistent Throughout Oncology Trials

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Objective

Cost-effectiveness analyses of oncology treatments require accurate and uniform reporting of data relating to adverse events (AEs) and deaths. The availability of appropriate and robust data to populate model parameters, however, is sometimes quite limited (1), as publications from clinical trials may be lacking in detail or consistency.

Here, we sought to explore the consistency of reporting of AE data in peer-reviewed oncology trial publications of previously untreated diffuse large B-cell lymphoma (DLBCL) and relapsed/ refractory small cell lung cancer (SCLC).

Introduction

The demand for economic models evaluating cancer treatments is increasing (1). As innovative, high-cost cancer therapies continue to come to market, healthcare decision-makers struggle for ways to manage their budgets while providing the best care possible to patients with cancer. Decisions about adoption of a new treatment or technology should consider both clinical benefits of the product and potential harms, such as AEs (2).

Health technology assessments are being used increasingly by decision-makers to help make treatment recommendations; they comprise of a systematic review of the clinical effectiveness evidence, and an economic evaluation. The inclusion/ exclusion of AEs in economic models can potentially affect cost-effectiveness of a new treatment (2).

Fig. 1: Factors influencing healthcare decision-making

DLBCL is a cancer of B cells, white blood cells responsible for producing antibodies. It is the most common type of non-Hodgkin lymphoma among adults (3). SCLC accounts for 12–16% of lung cancer cases (4). It usually presents in the central airways – the bronchi connecting the trachea to the lung – and infiltrates the bronchial submucosa (5). Published economic models of DLBCL and SCLC have included costs for AEs like anemia (6), or for management of AEs (7).

Methods

The reporting of AEs and deaths was evaluated in articles relating to trials in previously untreated DLBCL, and relapsed/ refractory SCLC, that were published in the last 10 years. We chose two very different cancer types – a previously untreated blood cancer, and a relapsed/ refractory solid cancer – in order to investigate the reporting of AEs across various cancer indications.

Methods (continued)

All relevant studies were data extracted to determine whether AEs were addressed at all, whether criteria used to report AEs were specified, and whether the rate and severity of AEs was clearly stated. In addition, it was examined whether the total number of deaths and/ or the number of treatment-related deaths was reported. We used an adapted version of the Consolidated Standards of Reporting Trials (CONSORT) to evaluate the reporting of AEs (8); see Table 1 for details.

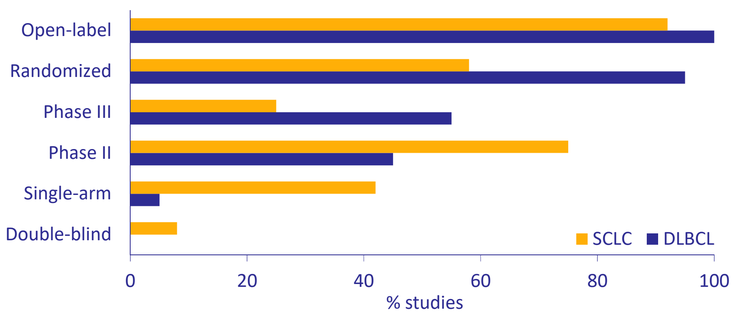
Table 1: Adapted CONSORT guidelines

Elements included in current analysis
(1) Title/abstract indicates harms are addressed in study.
(2) Introduction states harms are addressed in study.
(3) Article specifies whether reported AEs encompass all recorded events or only a selected sample.
(4) Article specifies instrument/scale utilized to categorize AEs.
(5) Article specifies time frame of surveillance for AEs.
(6) Article specifies whether early stopping rule was used for toxicity.
(7) Article specifies whether recurrent events in the same patient are counted as separate or single events.
(8) Article reports reasons for treatment discontinuation.
(9) Article reports whether deaths related to adverse events occurred.
(10) Article specifies which patients were evaluable for toxicity.
(11) Article reports absolute numbers of adverse events (rather than percentages alone).
(12) Article does not only report adverse events observed above a certain frequency or rate threshold (e.g., > 5% or > 10% of participants).
(13) Article does not combine adverse events of varying severity.
(14) Article does not use generic or vague descriptors of toxicity (e.g. “the regimen was generally well tolerated”).

Results

20 trials were identified for previously untreated DLBCL (A-T) and 12 trials were identified for relapsed/ refractory SCLC (I-XII). All DLBCL studies were open-label trials, and the majority (95%) were randomized; eleven studies (55%) were phase III trials. Most SCLC studies (92%) were open-label trials, however, only seven studies (58%) were randomized, and only three studies (25%) were phase III trials (Fig. 2).

Fig. 2: Characteristics of included trials



The criteria used to report AEs, and the rate and the severity of AEs that were included differed considerably across the publications. In the publications for DLBCL, three different criteria were used to report AEs, and 16 papers (80%) clearly stated which criteria were used.

The most commonly used instrument was the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE), followed by the Eastern Cooperative Oncology Group’s (ECOG) and World Health Organisation’s (WHO) Common Toxicity Criteria.

The severity of AEs reported ranged from ‘all AEs’ to ‘grade 3–4’, and the frequency of AEs ranged from ‘all’, to ‘common AEs’. As a result, AEs were reported in 15 different ways; details are shown in Table 2.

Results (continued)

Table 2: Reporting of AEs in prev. untreated DLBCL

Number of studies presenting AEs	20
Number of criteria used	3
Number of studies not specifying criteria	4
Ways of reporting AEs/ severity of AEs included	Any, any in ≥15% of patients, toxicity related to treatment, toxicity secondary to treatment, by grade, grades 0-4, grades 1-4, grades 1-3, grade 3 to 4, grade 3 or 4, grade 3 or 4 in ≥5% of patients, grade ≥3, grade ≥3 in ≥5% of patients, serious, AE of special interest
Number of ways of reporting AEs	15

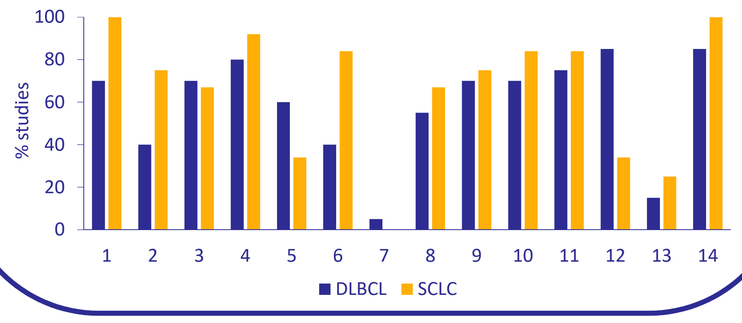
For SCLC, only one instrument (NCI-CTCAE) was used to categorize AEs, and most publications (92%) clearly stated this. AEs were reported in nine different ways, with the severity of the AEs ranging from ‘all’ to ‘grade ≥3 occurring in ≥5% of participants’. Details are presented in Table 3.

Table 3: Reporting of AEs in relapsed/ refractory SCLC

Number of studies presenting AEs	12
Number of criteria used	1
Number of studies not specifying criteria	1
Ways of reporting AEs/ severity of AEs included	Any, by grade, grade 3 or 4 in ≥10% of patients, grades 1 to 2, grades 3 to 4, grade ≥2, grade ≥3, grade ≥3 in ≥5% of patients, worst toxicity experienced by patient
Number of ways of reporting AEs	9

The number of deaths was not always reported. In DLBCL, 80% of publications (16 studies) reported the total number of deaths, and 70% (14 studies) reported the number of treatment-related deaths. For SCLC, eight studies (67%) reported total deaths, and six studies (50%) specified toxicity- or treatment-related deaths. A summary of the CONSORT analysis is shown in Fig. 3 (please refer to Table 1 for numbering).

Fig. 3: Reporting of AEs in accordance with adapted CONSORT guidelines



Conclusions

- Within and across oncology indications, there is variation in the criteria used to report AEs.
- The detail to which AEs are reported is very variable. Often terms such as ‘common AEs’ are used without being defined, and AEs of varying severity are combined (>75% of studies).
- There is a lack of clear reporting of deaths and treatment-related deaths.
- Greater consistency in the reporting of AEs and deaths would improve quality of the data being entered into economic models.

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