

A Systematic Review of Utility Values for Chemotherapy-Related Adverse Events

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Abstract

Background Chemotherapy offers cancer patients the potential benefits of improved mortality and morbidity but may cause detrimental outcomes due to adverse drug events (ADEs), some of which requiring time-consuming, resource-intensive and costly clinical management. To appropriately assess chemotherapy agents in an economic evaluation, ADE-related parameters such as the incidence, (dis)utility and cost of ADEs should be reflected within the model parameters. To date, there has been no systematic summary of the existing literature that quantifies the utilities of ADEs due to healthcare interventions in general and chemotherapy treatments in particular.

Objective This review aimed to summarize the current evidence base of reported utility values for chemotherapy-related ADEs.

Methods A structured electronic search combining terms for utility, utility valuation methods and generic terms for cancer treatment was conducted in MEDLINE and EMBASE in June 2011. Inclusion criteria were: (1) elicitation

of utility values for chemotherapy-related ADEs and (2) primary data. Two reviewers identified studies and extracted data independently. Any disagreements were resolved by a third reviewer.

Results Eighteen studies met the inclusion criteria from the 853 abstracts initially identified, collectively reporting 218 utility values for chemotherapy-related ADEs. All 18 studies used short descriptions (vignettes) to obtain the utility values, with nine studies presenting the vignettes used in the valuation exercises. Of the 218 utility values, 178 were elicited using standard gamble (SG) or time trade-off (TTO) approaches, while 40 were elicited using visual analogue scales (VAS). There were 169 utility values of specific chemotherapy-related ADEs (with the top ten being anaemia [34 values], nausea and/or vomiting [32 values], neuropathy [21 values], neutropenia [12 values], diarrhoea [12 values], stomatitis [10 values], fatigue [8 values], alopecia [7 values], hand-foot syndrome [5 values] and skin reaction [5 values]) and 49 of non-specific chemotherapy-related adverse events. In most cases, it was difficult to directly compare the utility values as various definitions and study-specific vignettes were used for the ADEs of interest.

Limitations This review was designed to provide an overall description of existing literature reporting utility values for chemotherapy-related ADEs. The findings were not exhaustive and were limited to publications that could be identified using the search strategy employed and those reported in the English language.

Conclusions This review identified wide ranges in the utility values reported for broad categories of specific chemotherapy-related ADEs. There were difficulties in comparing the values directly as various study-specific definitions were used for these ADEs and most studies did not make the vignettes used in the valuation exercises

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available. It is recommended that a basic minimum requirement be developed for the transparent reporting of study designs eliciting utility values, incorporating key criteria such as reporting how the vignettes were developed and presenting the vignettes used in the valuation tasks as well as valuing and reporting the utility values of the ADE-free base states. It is also recommended, in the future, for studies valuing the utilities of chemotherapy-related ADEs to define the ADEs according to the National Cancer Institute (NCI) definitions for chemotherapy-related ADEs as the use of the same definition across studies would ease the comparison and selection of utility values and make the overall inclusion of adverse events within economic models of chemotherapy agents much more straightforward.

Key Points for Decision Makers

- There is a substantial body of literature reporting the utility of chemotherapy-related adverse drug events (ADEs), using various definitions and study-specific vignettes, resulting in difficulties in comparing the values directly
- It is recommended that a basic minimum requirement be developed for the transparent reporting of study designs eliciting utilities, incorporating key criteria such as reporting the development of vignettes and presenting the final vignettes as well as valuing and reporting the utilities of the ADE-free base states
- It is also recommended for studies to define chemotherapy-related ADEs according to the National Cancer Institute definitions as standardization would ease the comparison and selection of utility values for chemotherapy-related ADEs

1 Introduction

Chemotherapy has been the mainstay of cancer treatment for many decades, offering various patient benefits, such as a possible cure, extension of survival and symptomatic relief, depending on the stage of the cancer. Chemotherapy treatment may be supplemented with other treatment modalities such as surgery and/or radiotherapy as well as hormone therapy, to remove and shrink the tumour and to reduce the risk and/or rate of recurrence, respectively. In recent years, a new treatment option has emerged with the use of immunomodulating drugs for cancer patients [1], which have a different and more specific mechanism of action than chemotherapy. While the use of immunomodulating drugs in oncology is expanding, chemotherapy remains the main treatment option for many cancers.

Chemotherapy drugs, which are also known as anti-cancer or anti-neoplastic drugs, destroy rapidly growing

cells by interrupting the multiplication of dividing cells. These drugs can be used as sole or combination agents, usually as standardized regimens given in cycles of treatment. Chemotherapy is relatively non-specific and may damage both rapidly dividing cancerous and normal cells. Theoretically, cyclical pulses of treatment should allow normal (non-tumour) cells to recover in between cycles while maintaining the cytotoxic effect on cancer cells. Despite the use of treatment cycles, chemotherapy's non-specific mechanism of action often causes harm at therapeutic doses, with nearly all chemotherapy drugs causing some adverse drug events (ADEs). Most ADEs occur due to non-immunologic, rather than immunologic, aetiology [2] and these are sometimes known as dose-related or dose-limiting ADEs.

The National Cancer Institute (NCI) defines an ADE as: “an unfavourable medical occurrence (including symptom, sign, or disease including an abnormal laboratory finding) that happens during treatment with a drug or other therapy” [3]. Different chemotherapy drugs and regimens can cause different ADEs at varying severity. Examples of chemotherapy-related ADEs include damage to hair follicle cells, blood and bone marrow cells, digestive lining cells, nerve cells and the reproductive system causing alopecia, myelosuppression, mucositis, neuropathy and infertility, respectively. The NCI Common Terminology Criteria for Adverse Events [4] categorize different grades of chemotherapy-related ADEs according to severity (Grades 1 and 2 events are considered minor and Grades 3 and 4 events severe) and are based on abnormal laboratory findings and/or clinical symptoms. While most chemotherapy-related ADEs can be transient and time-limited, they can lead to increased morbidity, thus negatively affecting health-related quality of life (HR-QOL) [5] and may potentially reduce adherence to, and thus the effectiveness of, treatment. In some cases, chemotherapy-related ADEs can be associated with increased mortality [6]. In addition to the detrimental effects on the patient, ADEs may require time-consuming, resource-intensive and costly clinical management.

The introduction of new expensive agents has led to an increase in the costs of chemotherapy [7]. This alongside the existence of finite healthcare budgets have led to many economic evaluations of chemotherapy treatments [8], particularly cost-effectiveness and cost-utility analyses, which have become a key source of evidence for decision making to inform national funding and reimbursement decisions. While there is an implicit assumption that ADEs are very important in health technology assessments [9], there is currently no transparent and standard guidance on how to incorporate ADEs into economic models, unlike the situation for effectiveness and cost data. Given the high incidence and relative severity of ADEs in oncology specialties, it is possible that the associated costs and effects of

ADEs may have a material effect on the findings of economic evaluations. Ideally, current valuation of a healthcare intervention should take into account both the benefit and the disbenefit of treatment. In the case of chemotherapy, ADEs are one of the main sources of potential disbenefits and therefore ADE-related parameters such as the incidence, (dis)utility and cost of ADEs should be reflected within the model parameters. To date, there has been no systematic summary of the existing literature that quantifies the utilities of ADEs due to healthcare interventions in general and chemotherapy treatments in particular. This study aimed to summarize the current evidence base of reported utility values for ADEs that would be suitable for use in an economic evaluation of a chemotherapy agent.

2 Methods

This review focused on identifying published studies that have reported utility values for chemotherapy-related ADEs, generated from accepted [10] stated preference choice-based methods (standard gamble [SG] and time trade-off [TTO]). For completeness, the review also summarized values elicited using visual analogue scales (VAS), although this approach is not generally accepted to be a valid method for generating utility values because it does not include some consideration of the opportunity cost associated with valuing the impact of treatments [11]. The focus was specifically on chemotherapy treatment, rather than hormone therapy or immunomodulating agents such as monoclonal antibodies as these have completely different mechanisms of action and adverse event profiles compared with chemotherapy.

A structured electronic search strategy, which included terms for utility (such as utility and valuation), utility valuation methods (such as TTO, SG and VAS) and generic terms for cancer treatment (such as chemotherapy and cytotoxic), was used to identify studies reporting utility values of chemotherapy-related ADEs from two computerized databases, MEDLINE (1948–June 2011) and EMBASE (1980–June 2011). The search was restricted to English language publications. No specific search terms for adverse events were used in the search strategy as it is well recognized that electronic-based searches for literature about adverse events are problematic because data on adverse events are often sparse with various challenges in identifying relevant studies [9, 12] due to a lack of consistency in the keywords used. Relevant studies were instead identified manually from the abstracts found using the broad search strategy. The search strategy used is available as an Online Resource (Appendix 1). The inclusion criteria were: (1) studies that elicited utility value(s) or utility decrement(s) for chemotherapy-related ADE(s) and

(2) studies reporting primary data. Two reviewers (F. H. Shabaruddin, L.-C. Chen) screened and identified studies and extracted data independently. Any disagreements were resolved by a third reviewer (K. Payne).

3 Results

Of the 853 abstracts initially identified, 62 studies were obtained as full papers, and of these, 18 studies [13–30] met the inclusion criteria (see Appendix 2 [Online Resource] for a flow diagram of the review process). Table 1 presents a summary of the 18 studies, which collectively reported 218 discrete utility values of chemotherapy-related adverse events.

The primary aim of 14 studies was to elicit utilities [13–15, 17–21, 24–27, 29, 30], while four described the results of utility elicitation exercises, which were conducted as part of an economic evaluation [16, 22, 23, 28]. Fifteen studies elicited utilities for various ADEs, while three focused on specific ADEs of varying severity [13, 25, 29]. The number of participants estimating each utility value ranged from 10 to 202. Nine studies reported the response rate of the studies [13, 18, 20, 21, 25–27, 29, 30], which ranged from 15 % to 100 % participation. Seven studies reported the dates of data collection, which allowed for reference timelines [14, 15, 17, 19, 27, 29, 30], while 11 studies did not [13, 16, 18, 20–26, 28]. Thirteen studies reported their findings as utility values [13, 16–18, 20–23, 25, 27–30], four as utility decrements/increments [14, 19, 24, 26] and one as both values and increments/decrements [15].

All 18 studies used short descriptions (vignettes) to obtain utility values for chemotherapy-related ADEs. Eleven studies reported how the vignettes of the health states were developed [13–15, 20–22, 24–26, 29, 30], and one study referred to another publication that reported the development of the survey instrument [27]. The development of the health states in general, and ADE health states in particular, were reported in varying details by these 12 studies, with some providing detailed descriptions and others brief summaries. Health states were mainly developed based on reviews of the literature as well as consultations with clinical experts and sometimes patients. Only nine studies presented the final vignettes of the health states valued, seven within the published papers [13, 17–19, 24, 26, 29] and two as online appendices [15, 20]. Of these nine studies, seven reported the duration of the chemotherapy-related ADEs within the health states valued [15, 17–20, 24, 26], specifying the duration of the ADEs for every cycle of chemotherapy received or for the whole period of the health states valued.

There were 218 discrete utility values of chemotherapy-related ADEs identified from the 18 studies and these were

Table 1 Summary of the 18 studies reporting utility values of chemotherapy-related adverse events

Author (country)	Cancer type	Treatment under evaluation	CT-related ADEs assessed	Study sample (<i>n</i>)	Valuation method	Survey administration (date)	Development of health state	Duration of ADE(s) within health state(s)	How utility of ADEs reported
Best et al. [13] (USA)	Stage III CRC	Adjuvant oxaliplatin-based CT	1. Neuropathy (mild) 2. Neuropathy (moderate) 3. Neuropathy (severe)	Pts (49) Public (49)	TTO	Face-to-face interview (date NR)	Health state development survey, which was based on a review of previously developed health states, was completed by 34 pts	No duration stated for ADEs	Utility values
Beusterien et al. [14] (UK and Australia)	Advanced metastatic melanoma	No specific CT regimen	1. Hair loss (Grade I/II) 2. Skin reaction (Grade I/II) 3. Diarrhoea (Grade I/II) 4. Nausea/vomiting (Grade I/II) 5. Flu-like syndrome (Grade I/II) 6. Stomatitis (Grade I/II) 7. One in-/outpatient stay for severe toxicity (Grade II/IV) 8. 2–5 days hospitalization for severe toxicity (Grade III/IV)	Public: Australian (77) UK (63)	SG	Face-to-face interview (Dec 2007)	Health states were refined after an iterative review by 5 clinical experts, 2 oncology nurses, 3 QOL researchers and a pilot test with members of the general public	Vignettes NR	Utility decrements
Beusterien et al. [15] (UK)	CLL	No specific CT regimen	1. Nausea (Grade I/II) 2. Nausea/vomiting (Grade I/II) 3. Diarrhoea (Grade I/II) 4. Anaemia (Grade III/IV) 5. Pyrexia (Grade III/IV) 6. Pneumonia (Grade III/IV)	Public: England (59) Scotland (30)	SG	Face-to-face interview (Mar 2009)	An iterative process was used that incorporated input from the literature, pt web-based discussion forums, CLL physicians and pts	Specific duration stated for each ADE in vignettes for every cycle of CT	Utility values and utility decrements
Brown et al. [16] (UK)	Advanced breast cancer	Docetaxel, paclitaxel and vinorelbine-based CT	1. Peripheral neuropathy 2. Severe oedema 3. Severe skin condition 4. FN and hospitalized 5. Infection	Oncology nurses (30)	SG	NR (date NR)	NR	Vignettes NR	Utility values
Franic et al. [17] (USA)	No specific cancer	No specific CT regimen	1. PCNV (complete alleviation) 2. PCNV (partial alleviation) 3. PCNV (no alleviation)	Public: women (18)	1. SG 2. VAS	Face-to-face interview (Mar-June 2000)	NR	2 time frames for ADE health states: 3 days and rest of life	Utility values
Grunberg et al. [18] (USA)	No specific cancer	No specific CT regimen	1. PCNV	Pts and healthcare professionals (10)	SG	Face-to-face interview (date NR)	NR	Time frame for PCNV: 1 year	Utility values

Table 1 continued

Author (country)	Cancer type	Treatment under evaluation	CT-related ADEs assessed	Study sample (<i>n</i>)	Valuation method	Survey administration (date)	Development of health state	Duration of ADE(s) within health state(s)	How utility of ADEs reported
Grunberg et al. [19] (USA)	Breast cancer and lung cancer	No specific CT regimen	1. Limited nausea 2. Limited vomiting 3. Limited nausea and limited vomiting 4. Continuous nausea/vomiting	Pts (96)	SG	Face-to-face interview (Aug 2000 and Mar 2003)	NR	Time frame for: nausea (3 days or 1 year), vomiting (3 episodes or 1 year)	Utility increments/decrements (presented visually on a graph)
Havrilesky et al. [20] (USA)	Ovarian cancer	No specific CT regimen	1. Alopecia (Grade II) 2. Peripheral neuropathy (Grade I/II) 3. Stomatitis (Grade II) 4. Nausea and vomiting (Grade I/II) 5. Neutropenia (Grade IV) 6. Peripheral neuropathy (Grade III/IV) 7. Nausea and vomiting (Grade III/IV) 8. Fatigue (Grade III/IV)	Pts: women (13) Public: women (37)	TTO	Face-to-face interview (date NR)	Health state descriptions were based on exploratory interviews and focus groups with 2 gynaecologic oncologists, 1 gynaecologic oncology nurse clinician, and 2 women who had CT for ovarian cancer	Specific duration stated for each ADE in vignettes for every cycle of CT	Utility values
Hess et al. [21] (USA)	Advanced ovarian cancer	No specific CT regimen	9. FN	Pts: women on CT (28) Pts: women under surveillance (13)	1. VAS 2. SG	Face-to-face interview (date NR)	4 people (outcomes expert, medical oncologist, synaecologic oncologist and a lay person) completed the health state development survey	Vignettes NR	Utility values (presented visually on a graph)

Table 1 continued

Author (country)	Cancer type	Treatment under evaluation	CT-related ADEs assessed	Study sample (<i>n</i>)	Valuation method	Survey administration (date)	Development of health states	Duration of ADE(s) within health state(s)	How utility of ADEs reported
Hutton et al. [22] (UK)	Recurrent metastatic breast cancer	Docetaxel and paclitaxel-based CT	1. Peripheral neuropathy (severe) 2. Peripheral oedema (severe) 3. Sepsis	Oncology nurses (129); UK (30), other countries (<i>n</i> = NR)	SG	NR (date NR)	Development of health states involved iterative consultations with researchers, clinical experts, oncology nurses and experts in utility measurements (<i>n</i> = NR)	Vignettes NR	Utility values
Leung et al. [23] (Canada)	Anthracycline-resistant breast cancer	Docetaxel, paclitaxel and vinorelbine-based CT	1. Severe side effects	Public: women (25) Ps: women (25)	TTO	Face-to-face interview (date NR)	NR	Vignettes NR	Utility values
Lloyd et al. [24] (UK)	Advanced breast cancer	No specific CT regimen	1. FN 2. Diarrhoea and vomiting 3. Hand-foot syndrome 4. Stomatitis 5. Fatigue 6. Hair loss	Public (100)	SG	Face-to-face interview (date NR)	Development of health states based on various sources including literature review, exploratory interviews with expert physicians, 1 focus group with oncology specialist nurses, content validation interviews with 3 clinicians and pilot study with 5 members of the public	Specific duration stated for each ADE in vignettes for every cycle of CT	Utility decrements
Lloyd et al. [25] (UK)	No specific cancer regimen	No specific CT regimen	1. Anaemia (Hb 7.0–8.0 g/dL) 2. Anaemia (Hb 8.0–9.0 g/dL) 3. Anaemia (Hb 9.0–10.0 g/dL) 4. Anaemia (Hb 10.0–10.5 g/dL) 5. Anaemia (Hb 10.5–11.0 g/dL) 6. Anaemia (Hb 11.0–12.0 g/dL) 7. Anaemia (Hb 12.0+ g/dL)	Public (83) Ps (26)	1. SG (public) 2. TTO (pts) 3. VAS	Face-to-face interview (date NR)	Health state descriptions reviewed by 4 experts (nurse, 2 clinicians and a QOL expert), 5 pts interviewed for content validity. Health states finalized after pilot study with 5 members of the public	Vignettes NR	Utility values
Nafees et al. [26] (UK)	Metastatic non-small-cell lung cancer	No specific CT regimen	1. Neutropenia 2. FN 3. Fatigue 4. Diarrhoea 5. Nausea and vomiting 6. Rash 7. Hair loss	Public (100)	SG	Face-to-face interview (date NR)	Health states were developed based on a literature review, exploratory interviews (<i>n</i> = 8) and content validation interviews (<i>n</i> = 7). The final survey was reviewed by 2 psychometric experts and was piloted with 5 members of the public	Specific duration stated for each ADE in vignettes for every cycle of CT	Utility decrements

Table 1 continued

Author (country)	Cancer type	Treatment under evaluation	CT-related ADEs assessed	Study sample (<i>n</i>)	Valuation method	Survey administration (date)	Development of health state	Duration of ADE(s) within health state(s)	How utility of ADEs reported
Ness et al. [27] (USA)	CRC	No specific CT regimen	1. Significant side effects	Pts (40–81 respondents for each health state, with total 81)	SG	Face-to-face interview (Nov 1996–Mar 1997)	Health states were developed using focus groups, which identified and described important outcome states of CRC and constructed representative descriptions of these states	Vignettes NR	Utility values
Nguyen et al. [28] (USA)	Stage I nonseminomatous germ cell testicular cancer	No specific CT regimen	1. Cardiovascular disease 2. Secondary malignant neoplasms 3. Peripheral neuropathy 4. Otoxicity	Healthcare professionals: men (24)	1. VAS 2. SG	Administration method NR (date NR)	NR	Vignettes NR	Utility values
Ossa et al. [29] (UK)	No specific cancer	No specific CT regimen	1. Mild anaemia 2. Moderate anaemia 3. Severe anaemia	Public (106)	TTO	Face-to-face interview (Feb–Mar 2004)	Health states were developed based on consultation with 3 clinical experts and literature review, then validated by 3 oncology specialists and 6 pts	No duration stated for ADEs	Utility values
Shiroiwa et al. [30] (Japan)	Metastatic CRC	Oxaliplatin-based CT regimens (FOLFOX and XELOX)	1. FN (Grade III/IV) 2. Nausea and vomiting (Grade III/IV) 3. Diarrhoea (Grade III/IV) 4. Hand-foot syndrome (Grade III/IV) 5. Fatigue (Grade III/IV) 6. Peripheral neuropathy (Grade III/IV) 7. Stomatitis (Grade III/IV)	Public (159–201 respondents for each health state, with total 1,582)	1. SG 2. TTO	Internet survey (Jan 2008)	Health states were developed based on interviews with experts (<i>n</i> = NR) and literature review. First draft was reviewed by 2 experienced oncologists and 2 oncologic clinical research coordinators. Second draft was reviewed by clinical research coordinators	Vignettes NR	Utility values

ADE adverse drug event, CLL chronic lymphocytic leukaemia, CT chemotherapy, FN febrile neutropenia, Hb haemoglobin, NR not reported, PCNV post-chemotherapy nausea and vomiting, *pt(s)* patient(s), QOL quality of life, SG standard gamble, TTO time trade-off, VAS visual analogue scale

summarized and are presented in Appendix 3 (Online Resource). Of the 218 values, 178 were elicited using choice-based methods (SG or TTO), while 40 were elicited using VAS. The four studies that used VAS also employed choice-based methods (SG or TTO) to elicit utilities [17, 21, 25, 28]. There were 169 utility values of specific chemotherapy-related ADEs (with the top ten being anaemia [34 values], followed by nausea and/or vomiting [32 values], neuropathy [21 values], neutropenia [12 values], diarrhoea [12 values], stomatitis [10 values], fatigue [8 values], alopecia [7 values], hand-foot syndrome [5 values] and skin reaction [5 values]) and 49 of non-specific chemotherapy-related adverse events. Since patients receiving chemotherapy experience ADEs on top of their health states caused by the disease state and the treatment received, it is useful to know the utility value of the ADE-free base state in order to put the ADE utility value into context. All except six studies [16, 20–23, 25] reported the utility of the relevant ADE-free base states, which allowed the difference between the utility of the base state and the ADE state to be determined.

While there were wide ranges in the utility values reported for the broad categories of specific chemotherapy-related ADEs (see Appendix 3 [Online Resource]), it was difficult to compare the values directly as various definitions were used for the ADEs and most studies did not make the vignettes used in the valuation exercises available. Only four studies used standardized NCI grading and terminology to define the chemotherapy-related ADEs of interest, eliciting 37 utility values for Grades 1 and 2 ADEs and 49 values for Grades 3 and 4 ADEs [14, 15, 20, 30]. To illustrate the wide ranges observed, taking the example of chemotherapy-related nausea and vomiting, utility values between 0.36 and 0.942 were obtained using choice-based methods from diverse study populations for various definitions of this ADE. Study-specific vignettes for nausea and vomiting varied widely (when available), and therefore hindered direct comparisons. For febrile neutropenia, some comparison could potentially be made as vignettes were available for three studies [20, 24, 26], with all three describing inpatient treatment for febrile neutropenia. Two of the studies [24, 26] that were conducted by some members of the same research group with similar vignettes, using SG and surveying the UK public obtained utility values of 0.563 [26] and 0.565 [24] for febrile neutropenia, while another study [20] that used TTO and surveyed the US public obtained a utility value of 0.56. Such similar findings were not observed for severe (Grade 3 and 4) anaemia, with two studies that used SG and surveyed the UK public obtaining utility values of 0.583 [25] and 0.69 [15], while another UK-based study [29] that used TTO obtained a utility value of 0.48. It was difficult to compare these values as the two available vignettes [15,

29] varied, with only one [15] describing the treatment for anaemia. While it is difficult to directly compare the findings of different studies, utility values obtained from the three studies that focused on specific ADEs of varying severity [13, 25, 29] showed incremental increases as the ADEs of interest become less severe.

4 Discussion

This review identified a substantial body of literature reporting 218 utility values of chemotherapy-related ADEs. Of these, 178 values were elicited using choice-based methods (SG or TTO) and therefore could potentially be used as parameter inputs in an economic evaluation incorporating ADEs of a chemotherapy agent. In agreement with other published reviews of health state utility values [8, 31, 32], there were wide variations in the utility values obtained. The causes for this observed variation has previously been linked to a number of now well-accepted factors, such as the choice of valuation method, study perspective (*ex ante* or *ex post*) and sample population [8, 31, 32].

In this review, the 218 utilities of chemotherapy-related ADEs were elicited from various heterogeneous populations, such as members of the public, healthcare professionals and patients both with and without experience of the ADEs valued. Some methods guides suggest population-based preferences should be used to attach utility values to a set of health states generated from a patient population [10, 33]. The proposed benefit of this approach is that descriptions of health states are generated from a population of individuals who have some knowledge or degree of familiarity with the health states being valued. However, this is a challenge when valuing utilities of ADEs, as it is usually not feasible to identify a population of patients who have experienced the ‘ADE state’ being valued, particularly in the context of chemotherapy, which by its very nature is treating a patient population that may be too ill to contribute to research exercises. The researcher is likely, therefore, to have to rely on people without experience of the ADE being valued. Some of the studies identified in this review recognized this issue [15, 20, 26, 30]. One way to overcome this lack of familiarity with the ADE states valued is by using more innovative methods of describing ADEs and embracing different media, or multi-media formats, such as film clips and graphics, to describe the ADEs in the valuation exercise.

Current recommendations in several methods guides (such as those in the USA, the UK, Ireland, New Zealand, Thailand, Latvia, Lithuania and Estonia) [34] indicate that the preferred approach to value utilities is to base health state descriptions on published multi-attribute utility measures (such as the EQ-5D or SF-6D) and attach utilities to

these health states using a choice-based stated preference method, such as the TTO method. Commentators have noted how this approach may not be feasible in certain contexts [35, 36], such as when valuing ADEs, and suggested that the use of vignettes is a more practical and feasible option [36]. The use of vignettes to value the utility of chemotherapy-related ADEs in all 18 studies indicated that these researchers were in agreement with this observation. While the recommended use of vignettes may be limited to when data using validated HR-QOL measures are not available [36], a recent review of health-related utility values for economic models included in the National Institute for Health and Clinical Excellence (NICE) technology appraisals found that a third of the unique utility values in the models were elicited with vignettes (from 14 % of submissions) [8].

The use of vignettes poses another set of challenges that focuses on the requirement for a valid and reproducible set of utility values as vignettes are often study specific and the descriptions of ADEs in vignettes frequently vary between studies. Since differences in the descriptions of chemotherapy-related ADEs may affect the estimated utility values obtained, this adds another potential source of variation. Another concern relates to the face validity of vignettes, which depends on the rigour with which they are designed and requires extensive piloting including the use of robust qualitative methods such as in-depth interviews and focus groups [36]. The credibility of vignettes is also enhanced where the descriptions have been verified by an independent group [36], as was conducted by several studies identified in this review. Despite the obvious importance of describing how vignettes were developed, one-third of the studies identified did not report any detail on the development of vignettes, making it difficult to determine the validity and credibility of the survey instruments and the subsequent utility values obtained.

Half of the studies identified did not report the vignettes of the ADE states used in the valuation tasks. Considering the wide variations observed between published utility estimates for the same categories of specific chemotherapy-related ADEs, reporting the vignettes could help decision analysts appropriately select the utilities of chemotherapy-related ADEs to incorporate in economic models by allowing them to determine whether the ADE state valued adequately captures the health state represented in the analysis. This may be of particular importance with chemotherapy-related ADEs, where the health states are sometimes transient but often recurring and different ADEs may persist for varying periods of time. It is important for analysts to know how these ADEs were described in the vignettes as it may impact on the utility values obtained [29]. Furthermore, it is also not possible to assess whether the durations of the ADEs described were either logical or

realistic in terms of relevance to the treatment durations if the vignettes used to value ADEs were not available. While a fundamental component of the SG and TTO approaches is that respondents typically imagine that they are in the health state for the rest of their lives or for a set period such as 10 years, the description of ADEs, which are sometimes transient in nature, within the health states could include the duration of the ADEs per cycle of chemotherapy. In the current review, of the nine studies reporting the vignettes used, seven studies included the duration of ADEs in their vignettes, using different durations for different ADEs [15, 17–20, 24, 26], while the two other studies did not specify the duration of the ADEs within the health states valued [13, 29]. As both these studies investigated a specific ADE at varying severity [13, 29], it could not be determined whether assuming the same duration for different ADEs would be appropriate as well as if, and how, this assumption would affect the findings. For example, diarrhoea is usually a temporary ADE but neuropathy may persist for over a year. Furthermore, the expected harm from the ADE should also be clearly described, as an ADE that is transient but potentially life-threatening (Grade 3 or 4 neutropenia) should, in theory, generate a different (lower) utility value compared with one that causes transient discomfort without much risk of complications (Grade 1 or 2 alopecia). Grunberg et al. [19] clearly recognized the specific challenge associated with asking people to value minor ADEs compared with perhaps more easily valued severe ADEs, especially when using the SG valuation method. Ossa et al. [29] reported how some people refused to trade-off when asked to value the mild anaemia state using TTO. The use of adapted methods to value temporary health states has emerged in the literature, with a recent review that summarized available methods for valuing temporary health states concluding that there is presently no clear gold standard on the best method to use and additional research is needed to rigorously evaluate the relative performance of available methods and to determine whether, and to what extent, the duration of the health state affects the utility value obtained [37].

Combining health state utility values are of particular importance when dealing with chemotherapy-related ADEs as chemotherapy patients seldom experience only one ADE at a time. Despite this, only Shiroiwa et al. [30] mentioned the possibility of quantifying the utilities of multiple ADEs, by assuming utility was linear and additive. Beusterien et al. [14, 15] explicitly did not include health states with multiple ADEs because the authors thought it was not clear whether an additive or multiplicative model should be used. This decision reflects the current evidence base as there is no accepted method for how best to include utilities for health states that occur in the same person in an economic model [33]. One recent guidance has recognized this

as an important area for further research and in the meantime suggested the use of the multiplicative approach for the sake of consistency between health technology assessments [33]. However, a study conducted to empirically test the accuracy of the multiplicative estimator found that multiplication is not a good estimate and that further research is warranted before a specific alternative can be firmly recommended [38].

5 Limitations

This review was designed to understand the current evidence base of reported utility values for chemotherapy-related ADEs, with a specific focus on summarizing known values for use in economic evaluations. Due to the aim of providing an overall description of existing literature, the findings of this review were not exhaustive and were limited to publications that could be identified using the search strategy employed and those reported in the English language.

The published utility values identified were assessed in term of use in an economic evaluation, using the minimum criteria of whether the valuation methods were in line with economic theory and whether opportunity costs were considered. However, the quality of the 18 studies was not formally assessed, mainly because there was no published evidence-based guidance on how to value the utility of treatment-related ADEs and subsequently how to include them in economic models. Although no quality assessment was conducted, this review identified a complete absence of standardization between studies. Two key sources of variation that were identified related to the definitions of the ADEs and the description of the ADEs in the vignettes, such as the level of detail provided in the vignettes, how the vignettes were phrased and the duration of the ADEs within the health states. Descriptions of potentially important clinical aspects, such as the clinical management and the potentially cyclical nature of the chemotherapy-related ADEs, also varied between studies.

6 Recommendations

As it is currently recognized that the evidence base for the ideal utility valuation methods and approaches to how best to combine utility values requires further development, a guideline on *how* to conduct these studies may not yet be appropriate. However, a decision analyst selecting utility values for use in an economic model requires sufficient detail to inform the selection of the ‘correct’ value to use in the analysis and consideration of the potential impact of utility parameter uncertainty on the resulting incremental

QALYs estimated from the model. Currently, both the methods for utility elicitation and the incorporation of ADEs in economic models are neither standardized nor transparent. Further research is necessary to understand the impact of these variations, particularly in terms of if, and how, the methods used to quantify ADEs affect the values elicited; the way ADEs in general, and chemotherapy-related ADEs in particular, are incorporated within economic evaluations; and whether the results of published economic evaluations are sensitive to the utilities of ADEs and if they impact on resource allocation decision making. In light of these issues, a basic minimum requirement that could presently be developed would be a set of criteria for the transparent reporting of study designs eliciting utility values, which mirrors the early days of how to report the design and conduct of economic evaluations [39]. Key criteria that could be incorporated in such a checklist include reporting how the vignettes of the health states were developed and presenting the vignettes used in the valuation task as well as valuing and reporting the utility values of the ADE-free base states.

The second recommendation that emerged from this review relates to the various definitions used for chemotherapy-related ADEs within the same broad categories of ADEs. Study-specific definitions of chemotherapy-related ADEs complicate the explicit selection of utility values to include within an economic evaluation. In the future, it is recommended for studies valuing the utilities of chemotherapy-related ADEs to define the ADEs according to the NCI definitions for chemotherapy-related ADEs [4], as advocated in clinical trials. This standardization would ease the comparison and selection of utility values in economic models. Such a change would make the overall inclusion of adverse events within economic models of chemotherapy agents much more straightforward as the utility data can then easily be combined with incidence data, which are often defined within clinical trials according to the NCI definitions. To enable the seamless inclusion of chemotherapy-related ADEs within economic evaluations, with studies assessing chemotherapy-related ADEs in any aspect using the same definitions across the board, this recommendation could also be applied to studies describing the cost of chemotherapy-related ADEs.

7 Conclusion

This review identified wide ranges in the utility values reported for broad categories of specific chemotherapy-related ADEs. There were difficulties in comparing the values directly as various study-specific definitions were used for these ADEs and most studies did not make the vignettes used in the valuation exercises available. It is

recommended that a basic minimum requirement be developed for the transparent reporting of study designs eliciting utility values for chemotherapy-related ADEs, incorporating key criteria such as reporting the development of the vignettes and presenting the vignettes used in the valuation tasks as well as valuing and reporting the utility values of the ADE-free base states. It is also recommended, in the future, for studies valuing the utilities of chemotherapy-related ADEs to define the ADEs according to the NCI definitions for chemotherapy-related ADEs as the use of the same definitions across studies would ease the comparison and selection of utility values and make the overall inclusion of adverse events within economic models of chemotherapy agents much more straightforward.

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