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Title: The febrile neutropenia threshold for primary G-CSF prophylaxis in breast cancer

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Abstract:

Background: Current guidelines recommend primary (PP), as opposed to secondary (SP) prophylaxis with granulocyte-colony stimulating factors (G-CSF), for adjuvant breast cancer chemotherapy (AC) regimens associated with a febrile neutropenia (FN) risk of ≥ 20%. The adoption of PP G-CSF for FN prevention in various health care jurisdictions may be affected by its value for money (i.e. cost-effectiveness). **Design:** A systematic review of all cost-effectiveness / cost-utility analyses (CEA / CUA) involving PP vs. SP G-CSF for breast cancer AC was conducted to examine; i) cost-effectiveness of PP vs. SP; ii) FN threshold at which PP is cost-effective, and iii) potential impact of G-CSF efficacy assumptions on outcomes. **Results:** Of 114 publications identified, 5 CEA / CUA (USA = 1, UK = 1, Canada = 3) met the predefined inclusion / exclusion criteria. These CEA / CUA examined different AC regimens (TAC = 2; FEC-D = 1; TC = 2) and G-CSF formulations (filgrastim "F"= 4; pegfilgrastim "P" = 4) with varying baseline FN—risk (range 22 - 32%), —mortality (range 1.4 - 6.0%) and —utility (range 0.33 - 0.47) assumptions. Potential G-CSF benefit, including FN risk reduction with P vs. F, varied among models. Overall, relative to SP, PP G-CSF was not associated with good value for money, as per commonly-utilized CE thresholds at the baseline FN rates examined in most of these studies (n=4) including the consensus 20% FN threshold guideline. The value for money associated with PP vs. SP was primarily dependent on G-CSF benefit assumptions including reduced FN- mortality and improved BC survival. **Conclusions:** PP G-CSF for FN prevention in BC patients undergoing AC may not be a cost-effective strategy at the 20% baseline FN risk threshold as recommended by current practice guidelines.

Key Words: Febrile Neutropenia. G-CSF prophylaxis. Value for Money. Cost-Effectiveness. Breast Cancer.

INTRODUCTION

Febrile neutropenia (FN) is associated with significant morbidity, mortality risk, and cost.[1,2,3,4] It can also lead to adjuvant chemotherapy treatment delays and/or dose reductions that can potentially affect patient survival.[1,2] Patients developing FN are often prescribed granulocyte-colony stimulating factors (G-CSF) with subsequent treatment cycles in an attempt to reduce the risk of further FN events (secondary prophylaxis; SP) and maintain chemotherapy relative dose intensity (RDI).[5,6,7] Current practice guidelines recommend G-CSF from the first cycle of chemotherapy (primary prophylaxis; PP) if the predicted FN risk is 20% or higher.[5,6,7]

Globally, adjuvant chemotherapy for breast cancer often consists of taxane-based regimes such as TAC (Docetaxel, Doxorubicin, Cyclophosphamide), FEC-D (Fluorouracil, Epirubicin, Cyclophosphamide, Docetaxel) and TC (Docetaxel, Cyclophosphamide).[8,9,10] PP, as opposed to SP, is currently recommended for most patients treated with these regimens given the ≥ 20% FN risk observed with these regimens outside of clinical trials.[11] PP G-CSF could lead to lower FN-management costs and improved patient quality of life due to a reduction in FN event rate, and may also be associated with lower FN-related mortality rates and/or improved long-term cancer survival due to improved chemotherapy delivery.[12,13,14,15,16] PP G-CSF is also associated with significant drug acquisition costs that should be examined within the context of all potential downstream cost savings, quality of life improvements and survival benefits.[17]

The adoption of PP G-CSF for FN prevention in various health care jurisdictions could be affected by its value for money (i.e. cost-effectiveness).[18,19,20] Cost-effectiveness / cost-utility analyses (CEA / CUA) examine the incremental costs per life-year (LY) or quality-adjusted life-year (QALY) gained with an intervention, and can help address the question of "value in cancer care".[21] Interventions associated with incremental costs per QALY gained below commonly utilized cost-effectiveness (CE) thresholds (US$100,000[1] in the USA, £30,000 in the UK, and CAN$100,000 in Canada per QALY gained) are deemed to provide "good value for money".[20, 22] We conducted a systematic review to examine the "value for money" associated with PP vs. SP G-CSF for adjuvant chemotherapy in breast cancer.

METHODS

Literature search strategy

A literature search involving Pubmed and the Cochrane Database of Systematic Reviews was conducted on December 1, 2015 to identify all published CEA / CUA that examined G-CSF prophylaxis for FN risk reduction during adjuvant chemotherapy in breast cancer. The search included the following keywords: (economic, pharmacoeconomic, price, pricing, cost(s), cost analysis, or cost effective) AND (breast neoplasm(s) or breast cancer) AND (granulocyte colony-stimulating factor, G-CSF, filgrastim, or pegfilgrastim). In addition, references from all studies identified by search above were hand searched to identify potentially overlooked studies (backward search).

Inclusion and exclusion criteria

Economic evaluations of G-CSF prophylaxis (filgrastim or pegfilgrastim) for FN prevention that met all the following eligibility criteria were included; i) CEA / CUA studies, ii) adjuvant chemotherapy for breast cancer, iii) PP vs. SP G-CSF strategies, IV) outcomes reported in incremental costs per LY or QALY gained. Studies were excluded as follows; i) review articles and commentaries, ii) economic evaluations other than CEA / CUA, iii) publications in a language other than English, iv) mixed populations involving various cancers if outcomes not reported separately for breast cancer, v) G-CSF strategies involved different backbone chemotherapy regimens, vi) G-CSF prophylaxis was intended for bone marrow or peripheral-blood stem-cell transplantation, and vii) baseline FN rate examined was not stated / defined.

Data extraction & study aims

The selected studies were reviewed to extract and/or compute all relevant data pertinent to study methods, including key input parameters of G-CSF benefit (i.e. improved quality of life, lower FN-related costs, reduced FN mortality, and improved breast cancer survival), and cost-utility outcomes. All relevant data were extracted and/or computed by two authors (T.Y. and S.J.) with discrepancies resolved by consensus. The aims of this study were; i) to examine the value for money (i.e. cost-effectiveness) of PP vs. SP G-CSF for adjuvant chemotherapy in breast cancer, ii) to identify the FN rate at which PP G-CSF appearsto be a cost-effective strategy, and its value

for money at the consensus guideline 20% FN threshold, and iii) to evaluate the potential impact of G-CSF efficacy assumptions on outcomes.

RESULTS

Identified studies

The initial search returned 114 publications (Figure 1). Eighty were excluded based on the title and a further 29 after a more detailed review of the abstract / publication. Five studies met the predefined inclusion / exclusion criteria, and were included in this review (Table 1).[23,24,25,26,27] Backward search did not identify any other eligible studies. The included studies were conducted in different health care jurisdictions (USA = 1, UK = 1, Canada = 3), involved commonly utilized adjuvant taxane-based regimens (TAC = 2; FEC-D = 1; TC = 2), and all reported on incremental costs per QALY gained, albeit at different time horizons (range: 3-month to lifetime).

Study methods

All studies assumed a baseline FN risk greater than 20% (range 22 — 32%), and varying impacts of FN on quality of life and/or mortality (Table 1). All evaluations incorporated PP G-CSF for all chemotherapy cycles, with one [25] also examining PP G-CSF for the D cycles only (FN risk 14.8%) of FEC-D. All studies incorporated lower FN-related costs and improved patient quality of life due to reductions in FN event rate following G-CSF prophylaxis, but incorporated varying survival benefits due to lower short-term FN-related mortality and/or improved long-term breast cancer survival (Table 2). A public payer perspective was considered by all evaluations, and none accounted for indirect costs or took a societal perspective. Overall, upfront costs of G-CSF drug acquisition and downstream costs of FN management were highest in the USA and lowest in the UK (Table 3).

Value for money of PP vs. SP G-CSF strategies

PP G-CSF with filgrastim (Table 4) or pegfilgrastim (Table 5), was associated with both incremental cost and QALY gains relative to SP in all studies at the baseline FN rate examined in each. Overall, the computed incremental cost per QALY gained was higher than commonly utilized CE thresholds except in the evaluation [25] that examined PP G-CSF only for the D cycles of FEC-D

chemotherapy. In all other evaluations,[23,24,26,27] PP G-CSF was associated with a less than 50% (range 5 - 42%) probability of being a cost-effective strategy when judged against commonly utilized CE thresholds in the various jurisdictions studied. In sensitivity analyses, the value for money of PP G-CSF was primarily dependant on FN mortality rate assumptions,[23,25,26] baseline FN rate,[23,24,25,26] G-CSF costs,[23,24,25,26] and impact of PP on FN rate[23,26]. Conversely, FN utility [23,26] and chemotherapy characteristics,[26] including price and relative effectiveness, appeared to have relatively little impact on G-CSF value for money. Finally, FN management costs [23,25,26] had less significant [DR2]impact on G-CSF cost-effectiveness.

Impact of baseline FN rate and the consensus guideline 20% threshold

Unsurprisingly in all evaluations, higher FN rates were associated with improved cost-effectiveness. Except for the one study utilizing PP G-CSF for the D cycles of FEC-D chemotherapy only,[25] no study examining PP G-CSF at a baseline 20% FN rate found it to be associated with acceptable value for money although all found it to be a cost-effective strategy at higher FN rates. In one Canadian study,[26] PP G-CSF with filgrastim would meet a $100,000/QALY gained threshold at a FN rate > 28% assuming some loss of chemotherapy efficacy at lower chemotherapy doses, and at a > 22% rate assuming further loss of chemotherapy efficacy with every FN event regardless of subsequent chemotherapy doses. In the UK study,[24] PP G-CSF with pegfilgrastim would meet a £30,000/QALY gained threshold at a FN rate greater than 29%. Finally, in the US study,[23] a FN rate of 40% but not 20% was associated with CE less than the $100,000/QALY gained threshold ($49,000 vs. 156,000 / QALY gained, respectively).

Impact of G-CSF benefit assumptions

The cost-effectiveness of PP G-CSF appears to be primarily dependent on assumed survival benefits (i.e. reduced FN deaths and improved breast cancer survival). Indeed, in the one study that assumed no survival benefit,[27] PP vs. SP was associated with a very small 0.001 QALY gain and highly unfavourable cost-effectiveness estimates (ICER 2,348,924 per QALY gained) despite a significant 31% lower absolute FN event rate (1% vs. 32%, respectively). In the US and UK evaluations,[23,24] sensitivity analyses that tested the impact of PP G-CSF benefit on breast cancer survivalfound a positive relationship between survival benefit and value for money. Most

importantly perhaps, the impact of the assumed reduction in short-term FN deaths was more pronounced than the impact of any assumed improvements in long-term breast cancer survival. In one Canadian study for example,[26] the benefits [DR3]of PP G-CSF were primarily driven by FN-related mortality avoided (3.5 deaths [DR4]per 1000 treated) and not the breast cancer relapses prevented due to improved chemotherapy delivery. As well, the more favourable CE results reported in another Canadian study [25] likely partly reflect a higher assumed FN mortality risk (6%: range 4.5-7.6%) compared with other studies (range 1.4 — 3.6%), resulting in significantly larger numbers of FN-deaths avoided (7.3 - 10.8 and 8.7 - 12.5 per 1000 treated with filgrastim and pegfilgrastim, respectively) with no assumed improvement in breast cancer survival.

DISCUSSION

The adoption of various medical interventions depends partly on clinical benefit / risk profile and "value for money" among other factors[18,19] The assumed thresholds at which an intervention is assumed to be providing good value for money varies between nations as well as health authority jurisdictions and can also vary over time. The value for money of PP G-CSF in the identified studies was judged against commonly employed CE thresholds in the relevant jurisdictions (US$100,000 in the USA, £30,000 in the UK, and CAN$100,000 in Canada per QALY gained) but society and payers may adopt higher thresholds.[18,19,20] For example, the World Health Organization (WHO) defines the "value for money" of interventions relative to gross domestic product (GDP) per capita and defines these as being; i) highly cost effective (< GDP /capita), ii) cost-effective (1–3 times GDP / capita) and iii) not cost effective (>3 times GDP / capita).[22] Value for money should therefore be considered within the context of acceptable and perhaps evolving "willingness to pay" (WTP) thresholds.

The value for money of medical interventions depends on upfront cost and downstream benefit and includes cost savings due to the intervention as well as improvements in quality of life and survival. The identified CUAs, from the US, UK and Canada, with varying modeling assumptions and input parameters provide a unique opportunity to examine key drivers of the value for money associated with PP G-CSF across various health care jurisdictions.[23,24,25,26,27] Overall, and not surprisingly, the CE of PP G-CSF was affected by baseline FN risk and acquisition cost. The

adoption of PP G-CSF for higher FN risk scenarios as well as successful price negotiations aimed at lowering acquisition cost would improve the value for money further. Perhaps most importantly, despite the observed heterogeneity in study parameters and assumptions across the identified CUAs, the value for money of PP G-CSF appears primarily dependent on assumptions regarding potential short-term survival benefits achieved with PP G-CSF as opposed to improved quality of life or reduced costs. If the benefits of PP G-CSF were limited to improved FN costs and quality of life, PP G-CSF does not appear to be associated with good value for money.

Our systematic review and derived conclusions, have limitations. Firstly, and perhaps most importantly, the CUAs identified have incorporated different key assumptions regarding G-CSF benefits on short-term FN-related mortality and long-term cancer survival among other parameters. Indeed, the potential long-term survival benefit associated with PP G-CSF is not well defined to date, in particular with regard to long-term breast cancer specific survival due to improved chemotherapy delivery.[14,15,16] Clinical practice guidelines should attempt to provide clear consensus statements regarding the survival benefits achieved with PP G-CSF, if any. However, this heterogeneity in methods, assumptions and values can also be seen as a strength as it confirms the robustness of the overall findings of this review. Indirect costs such as lost productivity and caregiver costs were not considered in any of the CEA / CUAs identified. Value for money would be more favorable if these societal / indirect costs were also incorporated. A direct payer as opposed to a societal perspective, however, is routinely employed by drug funding regulatory agencies, such as the National Institute for Health and Care Excellence (NICE) and the pan-Canadian Oncology Drug Review (pCODR) - Expert Review Committee (pERC) in the UK and Canada, respectively, when addressing the value of cancer care.[28,29]

PP G-CSF in breast cancer appears to be associated with incremental costs per QALY gained that are higher than commonly utilized CE thresholds at the baseline FN risks and G-CSF assumptions examined in almost all evaluations incorporating adjuvant TAC, FEC-D and TC chemotherapy regimens. More importantly, PP G-CSF did not appear to provide good value for money at the 20% FN threshold currently recommended by practice guidelines [5,6,7] despite assuming a FN mortality benefit. PP G-CSF would be associated with better value for money at higher baseline

FN risk and/or higher WTP thresholds, and would also likely be cost-effective if it was also associated with significant improvements in long-term cancer survival due to improved chemotherapy delivery. Further clinical research is required to further elucidate the potential impact of PP G-CSF on acute FN-related mortality and long–term effects on cancer survival to more precisely determine the overall net cost-effectiveness of the intervention.

KEY MESSAGE

Current guidelines recommend primary prophylaxis with granulocyte-colony stimulating factors (G-CSF) for adjuvant chemotherapy regimens associated with a febrile neutropenia risk ≥ 20%. Primary prophylaxis with G-CSF for febrile neutropenia prevention in adjuvant chemotherapy for breast cancer may not be a cost-effective strategy at the current consensus guideline 20% FN threshold.

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DISCLOSURE

The authors have declared no conflict of interest

TABLES

Table 1: Study Characteristics

FIGURES

This figure shows a flow diagram of the search strategy and reasons for publication exclusion.

PP, primary prophylaxis; SP, secondary prophylaxis; G-CSF, granulocyte colony-stimulating factor; Δ, incremental.

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