Published in final edited form as:

Eur J Cancer Care (Engl). 2011 January ; 20(1): 72–76. doi:10.1111/j.1365-2354.2009.01136.x.

Bone pain from granulocyte colony stimulating factor: does clinical trial sponsorship by a pharmaceutical company influence its reporting?

Y. ALDAIRY, MD [Visiting Clinician],

Damascus, Syria

P.L. NGUYEN, MD, and

Division of Hematopathology, Mayo Clinic, Rochester, MN

A. JATOI, MD

Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA

Abstract

It is alleged that pharmaceutical companies sometimes unfairly present clinical trial results. To our knowledge, studies have not explored whether such alleged unfair reporting also occurs in the testing of palliative care agents in cancer patients, a particularly vulnerable group. Therefore, a systematic search was conducted to retrieve all published, prospective clinical trials that used granulocyte colony stimulating factor starting in 2003. Because granulocyte colony stimulating factor can cause severe bone pain – a concerning but historically under-reported symptom in cancer patients – this symptom was assessed to determine whether differences in reporting occurred based on pharmaceutical company-sponsorship. A total of 239 published clinical trials met the present study's eligibility criteria and were retrievable. Within this entire group of studies, 65 (27%) were pharmaceutical company-sponsored, and only 31 (13%) reported on bone pain. However, pharmaceutical company-sponsored trials reported on bone pain at a higher rate compared with other studies: 23% versus 9% ($P=0.005$), and this conclusion did not change after adjusting for dose, use of the slow release formulation and year of publication. The reporting of adverse events from cancer symptom control and palliative care interventions should be improved – especially in trials not sponsored by pharmaceutical companies.

Keywords

bone pain; pharmaceutical companies; granulocyte colony stimulating factor

A growing literature suggests that pharmaceutical companies unfairly influence the reporting of clinical trial results. Bero and others recently assessed 192 published, randomised controlled trials on statin drugs and observed that those studies funded by pharmaceutical companies were more likely to report favourable results (Bero *et al.* 2007). Similar alleged biases have been observed in trials on non-steroidal anti-inflammatory agents, calcium

channel blockers and antipsychotic drugs (Rachon *et al.* 1994; Stelfox *et al.* 1998; Heres *et al.* 2006). Predictably, these biases favour the drug that was manufactured by the pharmaceutical company sponsoring the trial.

In contrast, relatively few studies have examined the potential influence of pharmaceutical companies on cancer clinical trials and, particularly, on such trials that test palliative care interventions in this vulnerable group of patients. It should be noted, however, that pharmaceutical companies are currently providing total or partial funding to an estimated 44% of cancer clinical trials (Reichelmann *et al.* 2007). Are these companies also unfairly influencing how results are being reported from trials that test cancer palliative care interventions?

This study was undertaken to explore the above question. Novel supportive and palliative care interventions are being tested and used with increasing frequency in cancer patients (Lynn *et al.* 2002; Wolfe *et al.* 2008); but, at the same time, investigator-reported conflict of interest between investigators and pharmaceutical companies occurs in over 60% of all cancer clinical trials (Reichelmann *et al.* 2007). Incidentally, it should be noted that, at the time of this report, none of the investigators involved in the current study had received personal compensation or research funding from a pharmaceutical company in the preceding 3 years and that the current study was supported by non-pharmaceutical company funds (K24CA131099 from the United States' National Cancer Institute). In short, there is a strong rationale for exploring whether pharmaceutical company clinical trial sponsorship provides an unfair influence on the reporting of results from cancer supportive and palliative care trials, and the investigators for the current study appeared well positioned to explore this issue.

METHODS

Overview

This study focused on prospective clinical trials that tested the administration of granulocyte colony stimulating factor, an intervention used to increase the neutrophil count after cancer therapy. The primary aim of the present study was to report the frequency of a common adverse event of this agent, specifically bone pain, based on whether the clinical trial was reported to be sponsored by a pharmaceutical company or not.

Relevant clinical trials were systematically sought and reviewed to determine the percentage that reported the incidence of bone pain. The decision to focus on granulocyte colony stimulating factor rests in the fact that this palliative and supportive care agent is the most frequently used approach in the prevention of neutropenia and its consequences (Swanson *et al.* 2000). Additionally, the decision to focus on bone pain rests in the fact that pain in cancer patients has received increasing attention as a major, important symptom that historically has been inadequately elicited and treated (Cohen *et al.* 2003; Patrick *et al.* 2003; Goldberg & Morrison 2007). Thus, the need to assess bone pain in a modern-day clinical trial – particularly if patients are at increased risk for it – is obvious.

Search strategy

The study team used PubMed to search for all relevant articles published in 2003 or after. This year was chosen because it marks the publication of a seminal study that showed detrimental effects from another supportive and palliative care intervention, erythropoietin (Henke *et al.* 2003), thus emphasising the importance of scrutinising the safety of even symptom control and palliative care interventions. The search terms ‘clinical trial’, ‘cancer’ and ‘granulocyte colony stimulating factor’ were combined and used to generate a list of publications. Articles not published in English were excluded.

Data extraction

All eligible articles were initially reviewed in abstract form by members of the study team to confirm that each represented a prospectively conducted clinical trial. Articles that did not comply with these inclusion criteria were excluded. Thereafter, the full publication was reviewed in depth and the following information was extracted: (1) further confirmation that the clinical trial did in fact represent a prospective clinical effort that included the administration of granulocyte colony stimulating factor; (2) whether or not bone pain was reported; (3) whether or not a more general category of ‘pain’ was reported; (4) whether or not the dose of granulocyte stimulating factor or pegylated (slow release) granulocyte stimulating factor had exceeded that provided in the package insert; (5) whether or not the pegylated (slow release) formulation had been prescribed, (6) year of publication; and (7) the funding source for the clinical trial (pharmaceutical company source, a non-pharmaceutical company source, or no reported source).

Inconsistent reporting methods across trials made it impossible to capture the percentage of patients with bone pain or its severity in each clinical trial in a meaningful manner. A deliberate decision was made to focus on all types of trials, including phase I, phase II and phase III studies because the study team wanted to be as thorough as possible in the assessment of adverse events. In addition, a deliberate decision was made not to assess whether each study was ‘positive’ or ‘negative’ based on the antineoplastic effects of the other agents being tested in view of the fact that studies had different primary end points and, in fact, were at times descriptive in nature.

Any trial with any degree of pharmaceutical company funding was categorised as a pharmaceutical company-sponsored study. It was thought that any degree of monetary support from a pharmaceutical company might theoretically enable that company to influence the study design.

Analyses

A chi-squared test was used to assess differences in the percentages of studies reporting bone pain based on reported funding source. A logistic regression model was used to generate a likelihood ratio *P* value to evaluate the effect of variables, such as dose of granulocyte colony stimulating factor tested in each study (greater than that recommended in the package insert or not), whether the pegylated formulation had been used and year of publication. These three variables were chosen because they might potentially affect the reporting of bone pain as a result of either a dose–response effect, an effect that might occur

as a result of the slow release action of the pegylated formulation, or changes in adverse event reporting practices over time (Framptom *et al.* 1994; Molineux 2004). A *P* value of <0.05 was considered statistically significant.

RESULTS

Characteristics of studies

A total of 532 articles were identified, and 281 met the a priori eligibility criteria for the present study. Other articles that did not meet the eligibility criteria were often reviews, retrospective analyses of previously acquired data sets or non-clinical studies. Of these 281 studies, the complete article was retrievable in 239 either electronically or by library retrieval. These 239 articles are the focus of the present study (Fig. 1). The vast majority of these studies entailed the administration of granulocyte colony stimulating factor in conjunction with myelosuppressive cancer chemotherapy.

Within this group of studies, 65 (27%) were sponsored by a pharmaceutical company, 100 (42%) had support only from other sources and 74 (31%) had no reported funding source (Table 1). These 'other' funding sources included such entities as the National Cancer Institute in the USA and private foundation sources. In addition, 2% of these studies had used a dose of granulocyte colony stimulating factor that was greater than that described in the package insert. Nineteen used the pegylated formulation, and two used both formulations. The number (%) of studies published in 2003, 2004, 2005, 2006 and 2007 was as follows: 61 (26%), 51 (21%), 50 (21%), 55 (23%) and 22 (9%) respectively.

Reporting of bone pain

A total of 31 clinical trials (13%) reported bone pain. The number of pharmaceutical company-sponsored trials that reported on bone pain versus those that reported bone pain but were funded by another or unreported source were 23% versus 9% (*P* = 0.005). In breaking down funding sources further in trials that reported bone pain, the number that were in part or totally funded by a pharmaceutical company versus another source versus an unreported source were 23% versus 11% versus 7% (*P* = 0.013). Of incidental note, assessing the presence of 'bone pain' in combination with 'pain', as denoted more generally, did not alter the foregoing conclusions.

In addition, the study team examined whether the dose of granulocyte colony stimulating factor had exceeded that recommended in the package insert, whether the pegylated formulation had been used and whether year of clinical trial publication modified study conclusions. Dose and year of publication did not exert a statistically significant effect on the reporting of bone pain (*P* = 0.39 and *P* = 0.66 respectively) whereas the use of the pegylated formulation was associated with a higher rate of bone pain reporting (*P* = 0.008). Nonetheless, pharmaceutical company-sponsored studies continued to report bone pain at a statistically higher rate compared with all the other studies even after these three variables were incorporated into the model (*P* = 0.038).

DISCUSSION

This study was conducted to explore whether clinical trials sponsored by pharmaceutical companies under-report bone pain, a major side effect of granulocyte colony stimulating factor. Surprisingly, although previous studies in non-cancer patients have concluded that pharmaceutical companies unfairly influence the reporting of clinical trial results, the present study observed the exact opposite: trials that were sponsored by pharmaceutical companies were in fact more likely to report bone pain and pain in general. These results suggest that in the setting of oncology supportive and palliative care, pharmaceutical companies are aware of the adverse event profiles of their agents and are more likely to be forthcoming in reporting such adverse events.

Another noteworthy observation is that the reporting of bone pain was overall very low. The majority of all the clinical trials assessed in the present study did not report on bone pain, and in fact only 13% of these trials provided such information. These findings suggest a lack of comprehensive assessment of adverse events in cancer clinical trials, even when therapy is aimed at cancer symptom control and palliation. One might argue that because bone pain is not a newly discovered side effect of granulocyte colony stimulating factor, re-reporting its occurrence is unnecessary. However, it should be noted that cancer clinical trials that test chemotherapy regimens, as a rule, report extensively on a variety of side effects that had already been reported with a given chemotherapy regimen. For example, it is well accepted that conventional chemotherapy can cause nausea and vomiting, and yet these adverse events continue to be elicited and reported in cancer clinical trials. Moreover, the recently reported erythropoietin adverse event data, which have led to drastic changes in clinical practice, also attest to the importance of comprehensive adverse event reporting (Tanne 2008).

Finally, one might question whether the more recent and concerning adverse event data on erythropoietin, as alluded to above, might have prompted pharmaceutical companies to begin to report adverse events from cancer symptom control and palliative care interventions more liberally, thus potentially putting the findings reported here at odds with those that preceded 2003. However, this observation seems unlikely. After adjusting for year of publication, study conclusions remained unchanged. In addition, presumably a large number of the clinical trials in this study were designed and developed well before 2003, thus suggesting that the results reported here were not influenced by the erythropoietin data.

Hence, the messages from the current study are evident. First, all published clinical trials should provide a thorough description of their funding source. Second, important symptoms, such as pain, should be elicited and reported in all cancer symptom control and palliative care trials, particularly if the intervention being tested is known or suspected to cause a certain symptom. Third, the reporting of all adverse events from cancer symptom control and palliative care interventions should be improved in all cancer clinical trials – but especially in trials that are not sponsored by pharmaceutical companies.

REFERENCES

- Bero L, Oostvogel F, Bacchetti P, Lee K. Factors associated with findings of published trials of drug–drug comparisons: why some statins appear more effective than others. *PLoS Medicine*. 2007; 4:1001–1010.
- Cohen MZ, Easley MK, Ellis C, Hughes B, Ownby K, Rashad BG, Rude M, Taft E, Westbrook JB. Cancer pain management and the JCAHO's pain standards: an institutional challenge. *Journal of Pain and Symptom Management*. 2003; 25:519–527. [PubMed: 12782432]
- Frampton JE, Lee CR, Faulds D. Filgrastim. A review of its pharmacologic properties and therapeutic efficacy in neutropenia. *Drugs*. 1994; 48:6137–6142.
- Goldberg GR, Morrison RS. Pain management in hospitalized cancer patients: a systematic review. *Journal of Clinical Oncology*. 2007; 25:1792–1801. [PubMed: 17470871]
- Henke M, Laszig R, Rube C, Schafer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C, Frommhold H. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomized, double-blind, placebo-controlled trial. *Lancet*. 2003; 362:1255–1260. [PubMed: 14575968]
- Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *The American Journal of Psychiatry*. 2006; 163:185–194. [PubMed: 16449469]
- Lynn J, Nolan K, Kabcenell A, Weissman D, Milne C, Berwick DM. Reforming care for persons at the end of life: the promise of quality improvement. *Annals of Internal Medicine*. 2002; 137:117–122. [PubMed: 12118967]
- Molineux G. The design and development of pegfilgrastim. *Current Pharmaceutical Design*. 2004; 10:1235–1244. [PubMed: 15078138]
- Patrick DL, Ferketich SL, Frame PS, Harris JJ, Hendricks CB, Levin B, Link MP, Lustig C, McLaughlin J, Ried LD, Turrisi AT 3rd, Unützer J, Vernon SW. National Institutes of Health State-of-the-Science Panel. National Institutes of Health State-of-the-Science Conference Statement: symptom management in cancer: pain, depression, and fatigue, July 15–17, 2002. *Journal of the National Cancer Institute*. 2003; 95:1110–1117. [PubMed: 12902440]
- Rachon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, Chalmers TC. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Archives of Internal Medicine*. 1994; 154:157–163. [PubMed: 8285810]
- Reichelmann RP, Wang L, O'Carroll A, Krzyzanowska MK. Disclosure of conflicts of interest by authors of clinical trials and editorials in oncology. *Journal of Clinical Oncology*. 2007; 25:4642–4647. [PubMed: 17925561]
- Stelfox HF, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. *The New England Journal of Medicine*. 1998; 338:101–105. [PubMed: 9420342]
- Swanson G, Bergstrom K, Stump E, Miyahara T, Herfindal ET. Growth factor usage patterns and outcomes in the community setting: collection through a practice-based computerized clinical information system. *Journal of Clinical Oncology*. 2000; 18:1746–1770.
- Tanne JH. FDA committee recommends restricting use of anti-anaemia drug in cancer. *BMJ*. 2008; 336:632.
- Wolfe J, Hammel JF, Edwards KE, Duncan J, Comeau M, Breyer J, Aldridge SA, Grier HE, Berde C, Dussel V, Weeks JC. Easing of suffering in children with cancer at the end of life: is care changing? *Journal of Clinical Oncology*. 2008; 26:1717–1723. [PubMed: 18375901]

Figure 1.
Consort diagram showing the ascertainment of eligible/retrievable studies.

Table 1
Study characteristics (%)*

	Pharmaceutical company-sponsored (n = 65)	Non-pharmaceutical company-sponsored (n = 100)	No reported source (n = 74)
Bone pain reported?			
Yes	15 (23)	11 (11)	5 (7)
Dose of granulocyte colony stimulating factor exceeds that in package insert?			
Yes	0 (0)	2 (2)	2 (3)
Just pegylated formulation used?			
Yes	9 (14)	7 (7)	3 (4)
Both used	1 (2)	1 (1)	0
Year of publication			
2003	19 (29)	20 (20)	22 (30)
2004	11 (17)	28 (28)	12 (16)
2005	17 (26)	17 (17)	16 (22)
2006	10 (16)	27 (27)	18 (24)
2007	8 (12)	8 (8)	6 (8)

* Numbers in parentheses denote percentages unless otherwise specified.