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A framework for assessing therapeutic innovation

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Budgetary restraints have been used to limit the freedom of medical prescription. This paper proposes a simple approach to the evaluation of costs and benefits. First the efficacy of a new approach is defined and compared with the best care with existing means. The incremental gain is then compared with the true cost of both procedures. The innovation should be adopted only where the gain is high and the cost low (or at least only minimally increased). In cases of debatable gain and costs, detailed cost–benefit analysis and quality of life studies are needed. We conclude that at present, 5-HT_3 receptor antagonists should only be used to control the acute phase of emesis.

Key words: 5-HT^3 antagonists, acute emesis, budget, cost, delayed emesis

Introduction

The availability of therapeutic innovations poses problems for health care professionals who have to decide whether there is any advantage in adopting them. This is not an easy task, because decisions have to be taken within the framework of existing, and even shrinking budgets, treatment programs and management structures. In cancer treatment, several recent discoveries have led to an explosion of costs; hematopoietic growth factors and anti-emetics are the latest examples. Ostensibly, physicians are faced with difficult choices. Limiting the debate to the field of anti-emetics an important factor is the patient's quality of life. However, this issue has not been properly addressed until now, and indirect measures (like decreased incidence of nausea and vomiting) are used to evaluate the impact of anti-emetics on quality of life. It remains to be proven whether enhanced quality of life, leading to better treatment compliance, will ultimately translate into a survival benefit.

A pragmatic model is proposed in this paper, which would allow an incremental approach in decision making to be made and would lead to an early assessment of the potential use of new treatments.

Assessment of the clinical benefits of innovation

The magnitude of clinical benefit needs careful evaluation, as it may be quite different among different groups of patients. Therefore, a study demonstrating advantage for a new approach has to be examined carefully to see whether the benefit is universal or could be attributed to specific patient subgroups. The importance of the problem has also to be evaluated. It would make no sense to adopt new, and usually costly, therapies for minor problems.

As depicted in Figure 1, once an important clinical benefit has been demonstrated it is essential to evaluate the likely impact on the total budget. Clearly, if there were a potential for greater benefit to the patient at low projected cost, the therapy would be readily adopted by health care providers. However, in the current budget-conscious climate, a potential low benefit at high projected cost would almost certainly lead to the therapy being discarded. This simplified approach has to be balanced by considerations which are beyond the scope of this paper. The importance of the gain may sometimes be relative and, for example, many would estimate that any gain in survival may be sufficient to justify

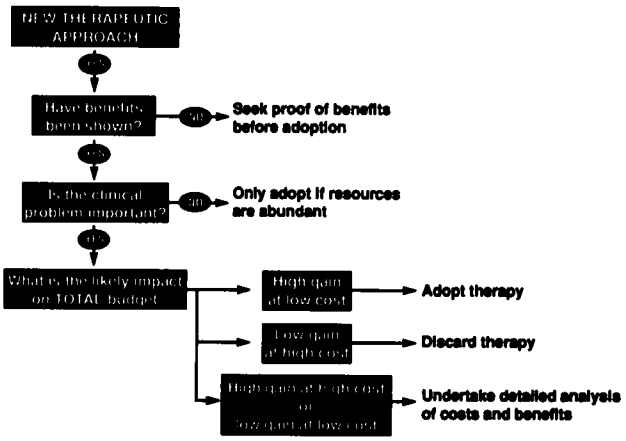

Figure 1. A pragmatic approach to decision making.

adjuvant chemotherapy with its costs in quality of life and money. The problem is worse with predictions of 'high gain at high cost' or 'low gain at low cost', where it becomes necessary to undertake a detailed analysis of both costs and benefits, as well as quality of life studies, discussed in other papers in this issue.[1–3]

Implications for 5-HT$_3$ receptor antagonist anti-emetics

Translating the issues discussed above to the field of 5-HT$_3$ receptor antagonists as anti-emetics, we must first decide whether benefit has been shown. This is beyond doubt.[4] However, as discussed later, this benefit has not been shown in all areas. The importance of the clinical problem has been demonstrated many years ago[5] and therefore the two basic questions have been answered positively.

The problem arises when one considers the result of adopting these new agents in daily practice (Figure 2). In acute-phase emesis (defined as arising at the latest 24 h after the start of chemotherapy), all the evidence suggests that the use of 5-HT$_3$ receptor antagonists leads to a high potential gain at relatively low incremental cost and should allow the therapy to become adopted by health care managers.[6,7] There would have been no problem if the development of 5-HT$_3$ receptor antagonists had been designed to address acute emesis properly. This has not been the case, as several agents were introduced (and received, surprisingly, regulatory approval) to be used with follow-up ingestion of 'preventative' tablets. As described in a recent paper, the unjustified use of serotonin$_3$ receptor antagonists led to an enormous economic burden for what many only consider 'patient comfort'.[8] Thus, in delayed-phase emesis, the use of 5-HT$_3$ receptor antagonists seems to lead to a low potential gain, if any, at high cost. Solid evidence of the value of these agents in delayed emesis must be found before this innovative therapy becomes adopted.[8–10]

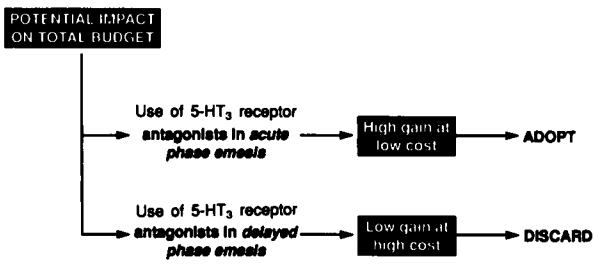

Figure 2. Implications of the pragmatic approach for the use of 5-HT$_3$ receptor antagonists.

Is this approach translatable in clinical practice?

The implementation of a new health policy is often a difficult task, at the hospital level, and it is important that the whole team, including senior physicians, pharmacists, junior doctors and nursing staff are involved in the decision-making process.[3] The key procedure in most centres is a clinical pharmacy committee, which evaluates the benefits and costs of a new drug along the lines depicted above. They would then determine the inclusion of a drug in the hospital formulary. However, the responsibilities of the committee should not stop there. It is important to monitor the use of the new drug through some control system. This is particularly true for non-toxic agents, which one feels free to prescribe even where there is little or no knowledge about the efficacy of the drug in some situations. This has been the case at the University of Geneva, where Kytril® registered for single daily use 'promoted' to three times daily, ignoring studies and registration packages (personal observation). This may lead to the choice of a single agent, with strict rules about its use. An interesting example of drug administration is illustrated in Figure 3. Ondansetron was introduced into hospitals at average doses between 16 and 24 mg. Then between November 1991 and July 1992, Glaxo attempted to introduce a lower dosage regimen for the drug. In general, clinicians ignored the company's recommendations, with the result that very little change took place throughout Europe in the dosage of ondansetron over that per-

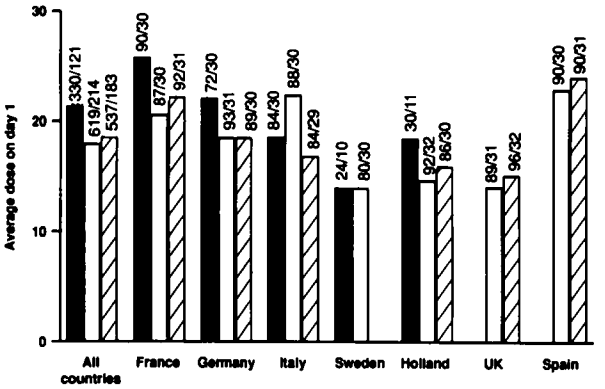

Figure 3. Ondansetron dosage used in practice has not declined significantly. ■, November 1991; □, April 1992; ▨, July 1992. Ratios are of number of patients/number of physicians.

iod (Figure 3). These data were collected by a telephone questionnaire of approximately 30 oncologists from each country.[11] Physicians were further contacted, until 30 who had used ondansetron had accrued for each country. Oncologists who agreed to take part were asked details of their three most recent patients treated with ondansetron for chemotherapy-induced nausea and vomiting. The doses listed in Figure 3 are the means of the total doses (intravenous plus oral) given on the first day of chemotherapy.

Conclusions

A logical approach to the introduction of new agents applied to serotonin$_3$ antagonists is important. There is no doubt that 5-HT$_3$ receptor antagonists represent an effective therapeutic innovation, and that they should be used in the prevention of acute chemotherapy-induced emesis, in situations of highly and many moderately emetogenic chemotherapies. Nevertheless, their use should be widely monitored, so that implementation into the hospital policy is carried out effectively, avoiding abuse and widespread unproven use of these agents.

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Appendix—Discussion

J Wagstaff (The Netherlands): There is an essential problem with the registration of drugs in oncology. The drug company carries out the clinical research and proves efficacy in terms of controlling vomiting. The regulatory authorities then ensure that this is accurate before allowing registration of that particular drug. Once registered, drugs become used more widely outside academic institutions. Doctors in these other institutions may not be quite so critical and may be persuaded by marketing and advertising to use drugs in situations where efficacy has not been definitely proven. This will produce quite marked increases in cost burdens for the health care system as a whole. It is imperative that the regulatory authority bears this in mind when they consider registration. A drug should be registered only for those clinical situations and dose schedules for which it was proven to be beneficial. Once that decision has been made it should then be an essential facet of healthcare policy at Government level that the doctor should be able to use that drug for a patient in that clinical situation. At the moment a drug may be registered but be too expensive for an individual patient. The doctor then has to justify use at his own hospital. This decision should have been made when the drug was registered. Perhaps open registration should be adopted.

MS Aapro (Switzerland): I think that this is a very important point. It is surprising that, so far, physicians have not had much influence on the studies which have led to registration. The decision lies with the bureaucrat, even if it does not make much sense to us as clinicians. We all know the battle we have had to stop placebo-controlled studies for antiemetics because we feel that they are unethical, but the bureaucrats still feel that they are ethical and that they should be conducted.

Unapproved use is a general problem. However, in clinical practice it is possible to use compounds in various alternative ways which are also effective. These variations may be difficult to register but may be supported by publication in a reputable journal. I

think we have to be careful not to become entangled by too much registration. Eventually we will all end up in court because we used a drug which is efficacious in breast cancer but was not registered for that disease. This happened in the States as you know.

C Latour (France): I would like to give a brief outline of the budgetary experience of 5-HT_3 receptor antagonists as a pharmacist at a small cancer treatment center in Lyon. The annual budget allocated for the use of the new anti-emetics in the centre for 1992 was 1.2 million French francs (Ff), out of a total drugs budget of 14 million Ff. In 1993, the anti-emetic drugs budget is expected to remain the same. As a comparison, the 1992 budget for cytostatic drugs was 5 million Ff, for antibiotics 3 million Ff and for G-CSF 1.5 million Ff. Conventional antiemetic drugs are a factor of 10 times less expensive than the newer 5-HT_3 receptor antagonists. There is no funding from the Health Ministry for any of these drugs and the center has to economize on the usage of cytostatic and anti-emetic drugs. We have reduced the antibiotic budget by adopting a general hospital formulary for this class. A similar general hospital protocol for anti-emetics has been adopted to obtain more rational use of anti-emetics.

The first step of the protocol investigates the suitability of the patient for inclusion into a clinical trial. This decision depends on previous exposure of a patient to chemotherapy and also on whether the patient is to receive either highly or emetogenic chemotherapy. There are four categories (or attitudes) employed at the center. In a typical protocol (Attitude 1), conventional drugs (metoclopramide plus a corticosteroid) are administered to patients receiving highly emetogenic chemotherapy. If the patient does not respond then second-line treatment with 5-HT_3 antagonists is initiated systematically. The other protocols are employed appropriately for the different patient categories. There is a subjective element in the procedure, allowing everyday practices to be taken into account. In conclusion, the introduction of the treatment protocols is leading to a much more efficient use of the limited resources in our center, which will ultimately benefit the patient, who is our most important consideration.

MS Aapro (Switzerland): Thank you Mr Latour. Your last remark is most important. The patient is the center of everything. It is all very well to discuss budgetary impact but if we have enough proof that our patient can benefit from something, then I think that we as physicians have a duty to fight, not for an industry, but for a patient's interests.

V L Barley (UK): Three brief comments. Firstly, you mentioned that costs of 5-HT_3 antagonists level off as people are using them more appropriately on larger numbers of patients and not using them where it is inappropriate. We have found this in our institution too. The costs this year are no higher than last year, although probably twice as many patients are receiving 5-HT_3 receptor antagonists. Secondly, there clearly are benefits from using treatment protocols and these should generally be encouraged, so that the use is optimal. We have found that by switching from inpatient to outpatient treatment we have been able to close beds and save money which can be transferred to the drugs budget to offset the higher costs of the 5-HT_3 receptor antagonists. The third point I would like to make is that many people have expressed frustration at discussing the higher costs of more effective therapy with administrators. However, there is increasing involvement of medical staff in the administration or management of oncology centres, and this is the way forward. If physicians are allowed to make the decisions on budgets then I think we are going to get a more effective use of the resources.

N Bosanquet (UK): From an economic perspective I would strongly support the approach just outlined by Dr Barley towards improved decision making in this area. However, I would be slightly suspicious of increasing the central regulation of drug use any further. It is already a fairly cumbersome process. Detailed conditions for drug use will lead to even more delay and may in fact discourage the kind of local innovation and search for local cost improvements which has just been suggested. As economists we should be quite open and say that the health-funding world is looking for oncologists to come up with more cost-effective ways of delivering the service. There is unlikely to be much new funding over the next 3 or 4 years and yet patient need is rising in many areas. I am well aware of many local problems but there will have to be a search for ways of reducing costs and delivering services in a more cost-effective way in order to fund these kinds of improvements. I know this is an unpalatable message but I am afraid that it is a realistic one.

MS Aapro (Switzerland): I fully agree that there should be protocols for the best way to control nausea and vomiting with anti-emetics. This reminds me of a study which was run all over Europe where clinicians were asked to use their choice of the best possible combination of anti-emetics and compare this with a 5-HT_3 antagonist. The results for this particular 5-HT_3 antagonist were good in this

situation, with the same percentage of responses as in other studies. However, what these very distinguished physicians thought was the best combination turned out to be a serious mistake. One benefit which has not been discussed is the relative ease of use of the 5-HT_3 antagonists, since at the correct dosage their use is not restricted by side effects. Therefore, patients are better protected from emesis than they have been in the past, since antiemetic control is much more consistent. This is an indirect benefit which should be calculated.

J Carmichael (UK): The 5-HT_3 antagonists are obviously very effective compounds and I agree with Dr Aapro that the quality of life of these patients is significantly enhanced when compared with standard regimens. In the very intensive, aggressive high-dose chemotherapy setting 5-HT_3 antagonists are effective, and in our institution we do not see the 3% increase in costs presented here. So it is cost effective in this group. We want to extend the use to more patients receiving moderately emetogenic chemotherapy. There is probably a way of limiting the costs here to below 10%, because we are overdosing these compounds at present as they have such a high therapeutic index. I think this is one area where we can extend the treatment to a far greater number of patients without significantly enhancing our costs.