Eur J Clin Pharmacol (1997) 53: 19–22

M. Lapeyre-Mestre · J. Gary · M. Machelard-Roumagnac
C. Bonhomme · R. Bugat · J. L. Montastruc

Incidence and cost of adverse drug reactions in a French cancer institute

Received: 10 February 1997 / Accepted in revised form: 29 April 1997

Abstract *Objectives*: The incidence and the cost of adverse drug reactions (ADR) in patients treated by cancer chemotherapy were assessed using hospital database records from 1993 in a French regional cancer institute. *Methods*: Patients with ADRs were identified using a list of ICD-9 codes describing potential adverse events. Direct medical costs for treating these ADRs were assessed according to the hospital system of claims data. *Results*: Among the 3429 in-patients hospitalized in 1993, we found 171 patients (5% of the population) who presented at least one ADR (3.5% of the total number of hospital stays). A total of 313 ADRs occurred in 256 hospital stays (3.5% of the hospital stays in 1993). Of the patients with ADRs 60.2% were female and their mean age was 51.5 years; 106 patients presented with at least one "serious" ADR according to the WHO definition. These ADRs occurred during 130 hospitalizations. In 7 cases, ADRs led to death. There was no relationship between age or sex and the seriousness of the ADR. Of the ADRs 91% was type "A" (predictable).

We estimated that the cost of "serious" ADRs was 1.8% of the global budget of the hospital. The average cost of ADRs leading to hospitalization was 33 037 French Francs at the current rate in 1993. This cost represented an additional cost of 32% of the overall cumulative yearly cost per patient in the institution.

Conclusion: This study emphasizes the medical and economic impact of the management of ADR in anticancer treatments.

Key words Adverse drug reactions, Anticancer drugs; cost, hospital

M. Lapeyre-Mestre (✉)
Department of Clinical Pharmacology, Faculté de Médecine,
37 Allées Jules Guesde, 31073 Toulouse Cedex, France.
Tel. +33-5-61-14-59-07; Fax +33-5-61-25-51-16;
e-mail lapeyre@cict.fr

M. Lapeyre-Mestre · J.L. Montastruc
Service de Pharmacologie Clinique,
Centre Midi-Pyrénées de Pharmacovigilance,
de Pharmacoépidémiologie et d'Informations sur le Médicament,
Centre Hospitalier Universitaire de Toulouse

M. Lapeyre-Mestre · J. Gary · M. Machelard-Roumagnac ·
C. Bonhomme · R. Bugat
Centre de Recherche et de Traitements Cancérologiques
Claudius Regaud, Toulouse, France

Introduction

In order to assess the medical and economic burden of adverse drug reactions (ADR) in patients treated in a cancer institute in France, we used the data obtained in the "Programme de Médicalisation des Systèmes d'Information" (PMSI). The PMSI is a French system for case-mixed classification for the management of public hospitals. The aim of the study was to ascertain the incidence of ADRs in cancer management, the seriousness and predictability of these ADRs and the outcome of ADRs in terms of medical and economic burden. Furthermore, we investigated whether PMSI could be used to identify all serious ADRs occurring in the hospital. Traditionally, the method of reporting ADRs in the Centre Claudius Regaud (CCR) has been a voluntary system that considered in a spontaneous incident report to the regional pharmacovigilance center, by phone or letter, generated either by the physician, the pharmacist, or the nurse who recognized and detected the event. The recorded ADRs may be either type A – predictable expected, and typically dose-dependent – or type B – unpredictable, unexpected, idiosyncratic, and typically dose-independent. According to the French unexpected drug reaction assessment, such reports are classified into five levels of intrinsic imputability: "very likely" (I4), "likely" (I3), "possible" (I2), "dubious" (I1), or "unlikely" (I0) [1].

Materials and method

The study was performed in a regional cancer institute located in Toulouse (southwestern France), the CCR, which is a 271-bed

hospital treating more than 2500 patients with cancer per year from the Midi-Pyrenees area. Since 1991, each hospital stay in CCR results in a standardized medical outcome summary (SMO) included in a registration form which is filed upon discharge from the hospital. This summary contains administrative data (name, sex, birthdate, and dates of hospital admission/discharge) and clinical data (patient diagnoses by the ICD-9 Classification and medical or surgical procedures undergone during the hospital stay). Administrative data and procedures are directly recorded by the medical and technical wards. Diagnosis data are recorded and coded by two specially trained secretaries from medical inpatient documents filed at each hospital discharge. Day care services were excluded from the study because medical data were not recorded in these services at the time of the study. Among the list of ICD-9 codes used during 1993, we selected those corresponding to a potential ADR: aplastic anemia, agranulocytosis, drug-induced neuropathy paresthesia, noxious effect of drug, cutaneous drug reaction, and anaphylactic shock.

All the 276 records identified as potential ADRs were examined to identify: (1) the reality of ADRs according to the WHO-CIOMS definition [2]: "a noxious and unintended event that occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions" and (2) the drug involved in the ADRs, the type of ADRs, the seriousness of the ADRs ("resulting in death, requiring inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, or life-threatening"). Data regarding the length of hospital stay were given by administrative data for the whole population of inpatients in 1993. Length of hospitalization related to ADRs was assessed as the difference between the beginning and the end of the ADR. The beginning of the ADR was the date of hospital admission due to ADR or the date of clinical or biological diagnosis of the ADR if it occurred during hospitalization. The end of the ADR was the date of the hospital discharge or the date of the normalization of the effect (date of laboratory examinations with normal results or end of the clinical symptoms reported by the physicians if the patient was not discharged from the hospital). Economic data were direct medical costs calculated for each hospital service by day rate according to the hospital system of claims data. The results are presented with mean and (standard deviation) and economic data are expressed in French Francs (FF) FF at the current rate in 1993.

Results

Prevalence of ADRs

During 1993, 171 patients (5% of the population of the 3429 in-patients in 1993) presented with 313 different ADRs occurring in 256 hospital stays (3.5% of the SMOs in a traditional hospital setting). In the population of patients with ADRs 60.2% were female, and the mean age was 51.5 (17.9), range 3–87 [63.9% and 54.5 (16.2) of the population of in-patients, respectively; not statistically significant]. During the same period, only 15 ADRs were reported by the traditional voluntary spontaneous report method. One hundred and six patients presented with 182 "serious" ADRs, according to the CIOMS definition. The occurrence and the seriousness of the reaction were not related to age or sex. The distribution of imputability scores was: concerning serious ADRs, 19.6% were "dubious" (I1), 67.9% "possible" (I2), and 12.5% "likely" (I3); and concerning nonserious ADRs, 6.6% were "dubious" (I1), 86.8% "possible" (I2), and 6.6% "likely" (I3). For both serious and nonserious reactions, the most common reactions were bone marrow suppression resulting in granulocytopenia, thrombocytopenia, or anemia, associated with sepsis or bleeding (Fig. 1).

Seriousness of ADRs

Serious ADRs involved 130 hospital stays and 106 patients. There were 106 admissions due to serious ADRs. In the other cases, serious ADRs prolonged hospitalization ($n = 20$), or were life-threatening without increase in length of stay ($n = 4$). In almost all cases, the drugs involved in serious ADRs were antineoplastic agents, except in 4 cases (methylene blue, paraffin, amitriptyline + chlorpromazine, noretisterone). Ninety one percent of serious ADRs were type "A" reactions. The "unexpected" ADRs were one case of anaphylactic shock with methylene blue, one case of pulmonary fibrosis with paraffin, one case of intraventricular hemorrhage with fluorouracil + cisplatinum, one case of colitis with docetaxel, one case of coma with ifosfamide + methotrexate + vepeside + mitoguazone, one of pancytopenia and coagulopathia with methyliodobenzylguanidine, one of esophagitis with adriamycin + cyclophosphamide + vindesine + bleomycine + prednisone and two cases of toxidermia with cisplatinum and

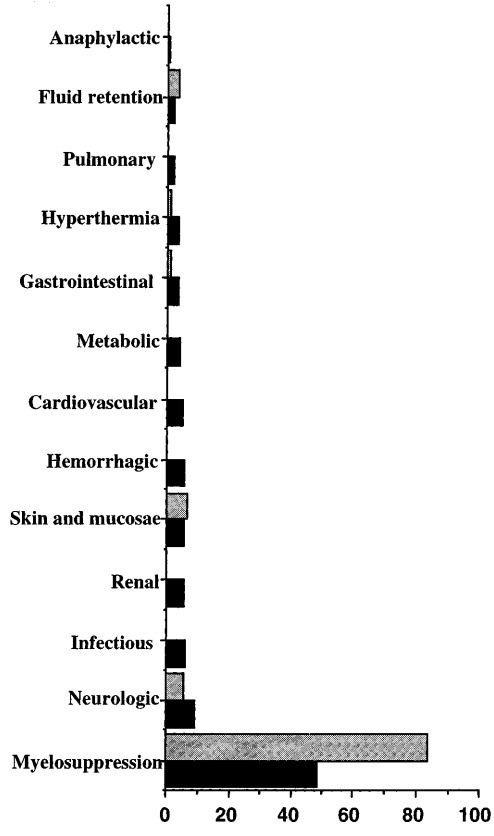

Fig. 1 Distribution in percentage of the main types of "serious" and (*black bars*) and "nonserious" (*stippled bars*) adverse drug reactions (ADRs) observed in 1993

with cisplatinum + adriamycin + fluorouracil. There were two cases of "unexpected" drug interactions: of bleeding with the interaction fluorouracil + vinorelbine + fluindione and of thrombocytopenia and decrease in prothrombin time with the interaction aminogluthetimide + hydrocortisone + acenocoumarol. Seven cases of ADRs led to death.

Concerning the cytotoxic drugs involved in serious ADRs, we examined the different protocol regimens which were associated with ADRs. Figure 1 presents the different cytotoxic protocol regimens which account for more than 4% of serious ADR and their relative frequency according to the total number of protocol regimens prescribed during 1993. The more frequently used regimens in 1993 (fluorouracil + vinorelbine: 8.1%; fluorouracil + adriamycin + cyclophosphamide: 6.5%; fluorouracil + epirubicin + cyclophosphamide: 4.5%) were less frequently involved in ADRs. All the protocol regimens involved in serious ADRs (Fig. 2) concerned palliative treatment, whereas 75% of the regimens administered during 1993 were palliative. Among the 130 ADRs observed, 107 required symptomatic treatment, which consisted in 9.2% blood transfusions and in 7.7% hematopoietic growth factors. Thirty-nine percent of the ADRs led to the definite withdrawal of the drugs involved in ADRs.

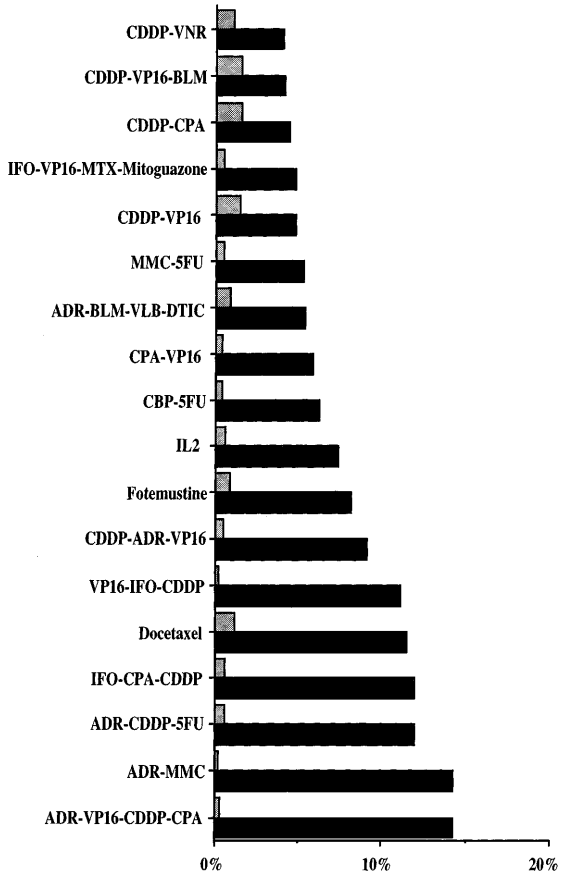

Fig. 2 Protocol regimens used in 1993 and involved in serious adverse drug reactions in (*black bars*) percentage of use in 1993 (*stippled bars*). *ADR* adriamycin; *BLM*, bleomycin; *CBP*, carboplatin; *CDDP*, cisplatin; *CPA* cyclophosphamide; *IFO* ifosfamide; *5FU*, fluorouracil; *MTX*, methotrexate; *MMC*, mitomycine C; *VLB*, vinblastine; *VNR*, vinorelbine; *VP16*, vepeside

Cost of serious ADRs

Hospitalizations with serious ADRs accounted for a total length of stay of 797 days (1.7% of the total in 1993). The total cost of treating drug-related illness evaluated by the claims data in the hospital was 3 435 867 FF (1.9% of the global budget of the hospital in 1993 and 15% of the drug budget). The mean cost to treat one ADR was 33 037 ± 610 FF per patient. Given the overall cumulative yearly cost per in-patient was 61 000 FF in 1993 in the institution, the additional cost to treat ADRs dramatically increased (plus 32%) the cost of care in the institution.

Discussion

The exact costs attributed to ADRs are not well known, but it has been suggested that ADRs can prolong hospital stays and add to health care expenditure [3–5]. Recent studies in several countries emphasize that drug-related morbidity and mortality should be considered as one of the leading diseases in terms of resources consumed [6–8]. Johnson and Bootman [8] suggested that the largest contributor to the total costs of drug-related problems was drug-related hospitalization. ADRs lead to 2%–7% of hospital admissions each year [9–13]. Moore et al. [5] emphasize that drug-induced diseases are a major cause of increased medical costs in France, with an average annual cost of drug-related illness of 30 000 FF in a population of Western France. Most of these ADRs are predictable and could or should be avoided. Thus, it is important to develop medical evaluations to provide increased quality of care and limit health expenses.

Many studies show that hospitalized patients have multiple risk factors predisposing them to ADRs: age, comorbidities, polymedications, etc. For these reasons, the need for hospitals to assume a more active role in ADR surveillance has been addressed internationally for many years by the WHO. In France, since beginning a system of pharmacovigilance in the early 1980s, primarily university hospitals have participated in the ADR reporting system. Our results show that using computerized medical record databases could extend the system in detecting ADRs, in addition to the traditional system of spontaneous reporting [9, 14].

Drug-related hospital admissions have been examined for many medical specialties, but few studies have been performed in cancer institutes. This area poses special interest, since drug-related admissions are believed to contribute significantly to rising hospital expenses and health care costs. Moreover, cytotoxic

treatments have a narrow therapeutic index, which increases the risks of iatrogenic disease [15]. In a study concerning the average cost of hospital readmissions for antineoplastic-induced toxicity in the USA [4], Johnson et al. concluded that there was an average net loss to the hospital of $4548 for each admission. Because most of the serious ADRs observed in our study required symptomatic treatment with granulocyte-stimulating factors, for example, we plan in a second step to study the results of medical and economic data recorded in 1995 in the same hospital to compare the effectiveness of different chemoprotective agents or supportive treatments which could be used to avoid predictable ADRs (hematopoietic growth factors, antiemetics, cytoprotective agents, etc.).

For patients with incurable cancer, the purpose of the treatment is to improve their survival in the best possible state of health. Our study determined that serious ADRs of cancer treatment concerned primarily patients with incurable cancer. Risks of treatment including mortality, nonlethal toxicity for bone marrow and other organs, and mild side effects of treatment such as nausea, vomiting, diarrhea, or anxiety could impair the outcomes of cancer treatment. More aggressive chemotherapy and host factors such as nutritional status, previous chemotherapy, or radiotherapy which may have altered the marrow regenerative potential and hepatic or renal dysfunction contribute to this situation. It seems necessary to ask whether new combinations of drugs, equipment and diagnostic procedures can be found to improve the prognosis of patients with incurable cancer [16]. In a recent study [17] comparing the effects of interleukin-2, interferon, and the combination of the two drugs in the treatment of metastatic renal cell carcinoma, the toxic death rate with interleukin-2 alone (7.9%) was higher than the response rate (6.5%). This result emphasizes that there is a choice between aggressive cytotoxic treatment with a risk equal to or higher than benefit and the use of a more supportive treatment in incurable patients which must be discussed.

A review of the medical records of patients for whom a serious ADR had been recorded shows that this event concerned 3% of the patients treated during 1 year in the institution. This percentage might be underestimated since some patients with ADRs could be admitted in another medical care facility. Severe but nonserious ADRs could have also induced considerable additional costs which were not included in the analysis. Though given this limitation, this study points out the high cost of these events in the hospital budget and offers an opportunity to assess the cost-effectiveness of cancer combination treatments and chemoprotective agents to improve the quality of care.

Acknowledgements The authors acknowledge physicians of the Centre Claudius Regaud for their participation to the record of medical data, and Paula Adams for her help in correcting the English.

References

1. Begaud B, Evreux JC, Jouglard J, Lagier G (1985) Unexpected or toxic drug reaction assessment (imputation). Actualization of the method used in France. Therapie 40: 115–118
2. World Health Organization. Collaborating Centers for International Drug Monitoring (1984) WHO publication DEM/NC/84.153 (E), WHO Geneva
3. Spreux A, Chichmanian RM, Castot A (1992) Economic impact of adverse drug effects. Therapie 47: 385–388
4. Johnson NE, Shoheiber O, Nash DB (1995) The costs of treating toxicities in cancer chemotherapy patients. Proc ASCO (Abstract)
5. Moore N, Briffaut C, Noblet C, Normand CA, Thuillez C (1995) Indirect drug-related costs. Lancet 345: 588–589
6. Schneider P, Gift M, Lee YP, Rothermich E, Sill B (1995) Cost of medication related problems at a university hospital. Am J Health Syst Pharm 52: 2415–2418
7. Hewitt J (1995) Drug related unplanned readmissions to hospital. Aust J Hosp Pharm 25: 400–3.
8. Johnson JA, Bootman JL (1995) Drug related morbidity and mortality: a cost of illness model. Arch Int Med 155: 1949–1956
9. Classen D, Pestotnik S, Evans S, Burke J (1991) Computerized surveillance of adverse drug events in hospital patients. JAMA 266: 2847–2851
10. Hallas J, Gram LF, Grodum E, Damsbo N, Brøsen K, Haghfelt T, Harvald B (1992) Drug related admissions to medical wards. A population survey. Br J Clin Pharmacol 33: 61–68
11. Lawson D, Beard K (1994) Intensive Hospital-based Cohort studies. In Pharmacoepidemiology, Second Edition, Ed Storm B pp 157–169
12. Prince B, Goetz C, Rihn T, Olsky M (1992) Drug-related emergency department visits and hospital admissions. Am J Hosp Pharm 42: 1696–1700
13. Chan TYK, Chan JCN, Tomlison B, Critchley J (1992) Adverse reactions to drugs as a cause of admissions to a general teaching hospital in Hong Kong. Drug Safety 7: 235–240
14. Hanesse B, Legras B, Royer RJ, Guillemin F, Briancon S (1994) Adverse drug reactions: comparison of two report methods. Pharmacoepidem Drug Safety 3: 223–229
15. Bodensteiner D, Doolittle G (1993) Adverse haematologic complications of anticancer drugs. Clinical presentation, management and avoidance. Drug Safety 8: 213–224
16. Jonsson V, Clausen SR, Hansen M (1995) Pharmacoeconomic aspects in the treatment of curable and incurable cancer. Pharmacoeconomics 8: 275–281
17. Négrier S, Escudier B, Lasset C, Savary J, Douillard JY, Chevreau C, Ravaud A, Peny J, Mousseau M and the French Immunotherapy Group (1996) The FNCLCC Crecy trial: Interleukine 2 + Interferon is the optimal treatment to induce responses in metastatic renal cell carcinoma. Proc ASCO (Abstract)