Clinical use, safety and effectiveness of novel high cost anticancer therapies after marketing approval: a record linkage study

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ABSTRACT

BACKGROUND: major clinical outcomes of anticancer drugs may differ between clinical trials and clinical practice. Administrative databases provide long-term information on safety and effectiveness of these drugs in large unselected populations and in selected subgroups of patients. In addition, these data provide complementary information on topics where evidence from randomized clinical trials is unavailable.

METHODS: this project will investigate 17 new targeted high cost drugs in Lombardy oncology practice between 2006 and 2010 using data from electronic healthcare databases. Specific objectives are: 1) to estimate the incidence of serious adverse events in clinical practice and their predictors; 2) to estimate survival and progression free survival and their predictors; 3) to compare major clinical outcomes according to different regimen of therapy. We will build a database by record linkage of several regional health service sources: the File F registry (in which the administration of the 17 drugs is recorded), the Regional hospital discharge forms (SDO) database, the drug prescription database, the outpatients' services database, and the Registry Office database. Subjects resident in Lombardy who received at least one prescription of these drugs from 2006 to 2010 will be considered. Complications warranting hospitalization will be derived from the patients' SDOs after the first drug administration. Vital status will be obtained from the Registry Office database.

RESULTS: we will provide estimates of the incidence of serious adverse events of novel anticancer therapies, and of overall and disease free survival in clinical practice, overall and in selected subgroups.

CONCLUSIONS: these data will contribute to a better effectiveness evaluation, particularly in patients under-represented in clinical trials.

Key words: Databases; Cancer therapy; Breast cancer; Colorectal cancer; Record linkage

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INTRODUCTION

Increased understanding of the molecular events involved in cancer development has led to the identification of several novel approaches to anticancer therapy [1]. Given the limitations of phase III trials evaluating these new agents' effectiveness and the excessive reliance on surrogate end-points, the added value of these drugs has been questioned [2]. Concerns have also been raised on their toxicity [3, 4]. It is unclear whether the frequencies of serious adverse events reported in clinical trials hold in clinical practice, in particular in patients excluded from clinical trials [5, 6]. Previous work has shown that the Lombardy Region administrative databases can provide valuable information on these issues [7-12].

In Italy, the National Health Service (NHS) provides drug coverage for all citizens (with level of reimbursement applied according to different drug classes) [13, 14], with the only exception of drugs administered within clinical trials. Each Region is responsible for planning, financing and monitoring health services within centrally-defined standards. Lombardy, a region of northern Italy with 9.5 million inhabitants (16% of country population), has defined a computerized database system to collect administrative information about health service since 1997 [15], also including data regarding the utilization of drugs approved for specific oncologic indications.

These large population-based datasets, primarily designed for administrative functions related to the provision of patient care, have also recently been used for epidemiological research, especially on drug use and side effects [11, 12, 16, 17]. Selected high-cost anticancer therapies are dispensed through the hospital pharmacy, and since 2006 registration of each dispensation on a electronic database (File F) is mandatory in order to obtain reimbursement from the NHS.

Healthcare databases are a uniquely useful source of data for pharmacoepidemiologic investigations and for comparative effectiveness research [18, 19]. The main advantages of such an approach are the representativeness of routine clinical practice in large populations, the long term follow-up, the coverage of all age groups, the low cost of data acquisition, and the validity of available information (i.e., avoidance or control of recall bias). These databases reflect real world clinical practice for large and unselected populations, and the data are already available with a validated scheme.

Up to now, existing administrative databases have been under-exploited in Italy and an evaluation of their potential for epidemiological studies on drug use in clinical practice is still lacking. Moreover, with the reference to the originality of the methodological approach, various study designs can be evaluated in order to verify the feasibility to analyse the comparative safety through healthcare databases.

Previous experience in the field: trastuzumab and bevacizumab

In a record linkage study based on the Lombardy Region-administrative databases, we investigated cardiac adverse events of trastuzumab for early breast cancer in the adjuvant setting in clinical practice [20], showing that the cardiotoxicity of trastuzumab varies considerably across subgroups of patients, and that the long term safety profile was less favorable than recorded in the largest clinical trial (Table 1).

In particular, out of 2 046 trastuzumab users, 53 (2.6%) experienced at least one hospitalization for a cardiac event, and there were two cardiac deaths. The cumulative risk of cardiotoxicity increased up to two years after starting treatment, reaching a plateau at 2.8%. The risk was low (0.2%) among young women, while in women aged >70 years, the incidence was approximately 10%, irrespective of cardiovascular risk factors. Age and history of cardiac disease were strong predictors of cardiotoxicity, with an hazard ratio of, respectively, 11.3 (95% confidence interval, CI 3.5-36.6) in women aged >70 years as compared to those <50, and 4.4 (95% CI 2.1-9.5) for those with history of cardiac disease, compared to those without.

Thus, cardiotoxicity is an important issue of concern regarding trastuzumab. Indeed, older patients and patients with comorbidities are often excluded or underrepresented in clinical trials designed to evaluate efficacy and safety of oncologic drugs. This has led to questioning whether their results can be transferred into clinical practice directly, and what is the performance of these drugs in older, less healthy patients.

The issue whether the cardiac events

TABLE 1

CARDIAC ADVERSE EVENTS (2006-2010) REQUIRING HOSPITALIZATION AMONG 2 046 TRASTUZUMAB USERS FOR EARLY STAGE INVASIVE BREAST CANCER. LOMBARDY, ITALY (DERIVED FROM BONIFAZI ET AL., 2013 [20])

	EVENT	
	YES N (%)	NO N (%)
At least one event	53 (2.6)	1 993 (97.4)
Cardiac death	2 (0.1)	
Myocardial infarction/ischemia	12 (0.6)	
Heart failure	28 (1.4)	
Rhythm disorders	21 (1.0)	
Cardiac dysfunctions	9 (0.4)	
AGE[a] (YEARS)		
<50	4 (0.5)	790 (99.5)
50-59	15 (2.6)	570 (97.4)
60-69	18 (3.7)	475 (96.3)
>=70	16 (9.2)	158 (90.8)
COMBINATION WITH PACLITAXEL		
Yes	8 (4.8)	160 (95.2)
No	45 (2.4)	1 833 (97.6)
PREVIOUS CARDIOVASCULAR RISK FACTOR[b]		
At least one risk factor	40 (4.0)	949 (96.0)
Diabetes	9 (7.3)	114 (92.7)
Hypertension	39 (4.4)	852 (95.6)
Dyslipidemia	14 (4.9)	271 (95.1)
Obesity	3 (15.0)	17 (85.0)
History of cardiac diseases[c]	9 (17.3)	43 (82.7)
No risk factor	13 (1.2)	1 044 (98.8)

[a] At breast cancer diagnosis
[b] Any risk factor before the beginning of trastuzumab treatment
[c] Any cardiac event before the beginning of trastuzumab treatment

observed in the study are in fact due to trastuzumab treatment or simply to the different baseline characteristics of the population remains open to quantification. The fact that the cumulative risk increased in the first two years after starting trastuzumab, and leveled off in the third year, after stopping treatment, suggests that most of the events observed during or soon after treatment might indeed be attributable to the drug.

The risk/benefits profile of trastuzumab should therefore be quantitatively assessed, and strategies to reduce cardiotoxicity, especially in older women and in women above age 50 with several cardiovascular risk factors, should be developed.

We also performed an analysis of adherence to the Italian Medicines Agency (AIFA, Agenzia Italiana del Farmaco) indications and safety of bevacizumab in Lombardy for the period 2006-2007 [9] (Table 2).

Treatment with bevacizumab was administered to 780 patients, of whom 81.7% (n=637) had metastatic colorectal cancer (mCRC). Among these, 37.8% (n=241) of patients received the drug in observance to AIFA indications. Overall, about 10% of patients had serious treatment-related toxicity (3.5% had fistulization, 2.8% venous thromboembolism, 1.9% hemorragia, and less than 1.0% intestinal perforation and arterial thromboembolism). The 1-year survival rate was 74.3% and the 2-year one was 39.2 %. The median survival time was 20.5 months, and there were no meaningful differences between gender and age groups.

TABLE 2

COMPLIANCE TO "AGENZIA ITALIANA DEL FARMACO" (AIFA) INDICATION[a] FOR THE BEVACIZUMAB (BV) USE IN METASTATIC COLORECTAL CANCER. LOMBARDY, ITALY, 2006-2007

TOTAL	N° (%) 637 (100)
METASTATIC DISEASE	
Diagnosis of metastasis prior to Bevacizumab treatment	605 (95.0)
Diagnosis of metastasis after Bevacizumab treatment	32 (5.0)
LINE OF THERAPY	
First	327 (51.3)
Second or more	265 (41.6)
Not defined[b]	45 (7.1)
REGIMEN OF THERAPY	
BV + FU based regimen	474 (74.4)
BV + FU/LV[c]	51 (8.0)
BV + FOLFIRI or IFL[d]	396 (62.2)
BV + FU ± IRINOTECAN	27 (4.2
BV without FU based regimen	100 (15.7)
BV + IRINOTECAN	71(11.1)
BV	29 (4.6)
BV ± FU ± IRINOTECAN	63 (9.9)
COMPLYING WITH AIFA INDICATION	241 (37.8)

[a] "First-line treatment of metastatic colorectal cancer in combination with Fluorouracil (FU)-based chemotherapy with or without Irinotecan"
[b] This includes also 32 subjects who did not satisfy the previous condition "metastatic disease"
[c] In 4 subjects the combination was followed by maintenance therapy with Bevacizumab alone
[d] In 30 subjects the combination was followed by maintenance therapy with Bevacizumab alone
(+): at least 75% of Bevacizumab prescriptions combined
(±): association in some administrations only

There is therefore a gap between bevacizumab approval indication and clinical practice pattern: overall, less than one-half of patients received bevacizumab in observance to regulatory indication. The main reason for non adherence to indications was use in second or advanced line of therapy. The incidence of serious adverse events and the survival rates of mCRC patients were similar to those reported in clinical trials.

An estimate of the incidence of cardio- and cerebrovascular adverse events of bevacizumab in real world condition, and the investigation of their predictors can provide useful information for clinicians in order to evaluate the "real-world" risk/benefit profile of bevacizumab.

General study objectives

Along the lines of the above described work, the general objective of the project is to investigate the utilization of 17 new targeted high cost drugs in Lombardy oncology practice between 2004 and 2012, namely bevacizumab, bortezomib, cetuximab, docetaxel, ibritumomab tiuxetan, irinotecan, oxaliplatin, paclitaxel, pemetrexed, rituximab, trastuzumab, fotemustine, alemtuzumab, temsirolimus, nelarabine, and panitumumab. Table 3 gives the number of prescriptions and the expenditure for 11 of these drugs in the period 2004-2007, stratified by sex.

Specific objectives are: (i) to monitor the use of these drugs in a large unselected population (ii) to evaluate adherence to the AIFA indications of use (iii) to estimate the incidence of serious adverse events in clinical practice and to investigate their predictors (iv) to estimate survival and progression free survival in clinical practice and to investigate

TABLE 3

NUMBER OF PRESCRIPTIONS AN EXPENDITURE (IN MILLIONS OF EURO) FOR EACH OF THE DRUG CONSIDERED, IN STRATA OF SEX. LOMBARDY, 2004-2007

		TOTAL	MEN	WOMEN
BEVACIZUMAB	No. of prescriptions Expenditure - M€	6 371 6.64	3 810 4.18	2 561 2.46
BORTEZOMIB	No. of prescriptions Expenditure - M€	6 723 7.08	3 754 4.02	2 969 3.06
CETUXIMAB	No. of prescriptions Expenditure - M€	12 442 11.03	7 549 6.96	4 893 4.07
DOCETAXEL	No. of prescriptions Expenditure - M€	28 937 15.07	11 358 5.79	17 579 9.29
IBRITUMOMAB TIUXETAN	No. of prescriptions Expenditure - M€	62 0.84	24 0.34	38 0.51
IRINOTECAN	No. of prescriptions Expenditure - M€	33 776 8.04	20 887 5.13	12 889 2.92
OXALIPLATIN	No. of prescriptions Expenditure - M€	48 033 19.38	28 785 12.06	19 244 7.32
PACLITAXEL	No. of prescriptions Expenditure - M€	47 184 15.72	3 145 1.1	44 039 14.62
PEMETREXED	No. of prescriptions Expenditure - M€	4 408 9.72	3 068 6.96	1 340 2.76
RITUXIMAB	No. of prescriptions Expenditure - M€	30 030 32.64	16 143 17.65	13 887 14.99
TRASTUZUMAB	No. of prescriptions Expenditure - M€	37 473 53.21	416 0.53	37 057 52.68
TOTAL	No. of prescriptions Expenditure - M€	255 439 179.38	98 939 64.71	156 496 114.67

their predictors (v) to compare selected aspects of the effectiveness according to different regimen of therapy, whenever possible.

METHODS

Sources of data

The study database will be built by record linkage of five regional health service databases, which include data on the use of health services by the beneficiaries of the NHS. Each record of these databases includes a personal identification code that identifies the NHS beneficiary uniquely and anonymously. The databases are:

1. The File F registry (currently available for the period 2004-2012), which contains all prescriptions of drugs administered directly in the outpatient setting and of selected novel high cost drugs administered in the inpatient setting or in Day Hospital (DH). The registration in the File F of these novel drugs administered during DH became mandatory in 2006. Each record includes a drug code, dosage and date of administration, and codes of the hospital and physician administering the drug.
2. The Regional hospital discharge forms (Scheda Dimissione Ospedaliera, SDO) database (1997-2012), which stores all Regional patient discharge records and reports clinical information about patients and their hospitalizations (both ordinary and DH), including demographic characteristics, admission

and discharge dates, the main and five secondary diagnoses (coded according to the International Classification of Disease 9, ICD-9), date and type of interventions, and hospitalization-related costs (coded according to the national diagnosis related group system - DRGs). SDOs referring to a chemotherapy also include information on whether the cost of the drug was compensated through the File F registry, or not.

3. The drug prescription database (2000-2012), which contains outpatients' prescriptions of medications reimbursed by the NHS.
4. The outpatients' services database (2000-2012), which contains all services performed to NHS recipients not in ordinary hospitalization or DH, including some chemotherapy or radiotherapy administration.
5. The Registry Office database of Lombardy (continuously updated), which includes information on vital status and, in case, date of death of Lombardy residents.

Population

Subjects who received at least one prescription of the 17 selected drugs from 2006 to 2010 and resident in the Lombardy Region are eligible. Users of selected high cost therapies will be identified through the file F, and a complete history of their health-care utilization will be obtained by linking the different pieces of information recorded into these databases using a unique personal identification code.

Data analyses

We will identify the diagnosis for which the drug treatment was prescribed by detecting a SDO reporting a diagnosis of cancer previous or contemporary to the first drug prescription. A SDO reporting a diagnosis of metastasis previous or contemporary to the first prescription will indicate metastatic disease. Type of treatment (first line, adjuvant, neoadjuvant, etc.) will be evaluated by detecting any records - SDO, File F or outpatient service - reporting chemotherapy administration between the first diagnosis of tumor and one month before the first prescription. Combination with other drugs will be defined as the presence of at least one File F record of another drug prescription within two days after or before each prescription. We will estimate survival rates using the information on vital status from the Lombardy Registry Office. To identify patients with selected chronic conditions (e.g. diabetes, dyslipidemia, obesity, cardiovascular, renal, respiratory, neurological and hepatic chronic diseases), we will retrieve hospitalizations reporting these diseases, and we will look for prescriptions of drugs related to these diseases in the outpatient drug prescription database, relying on a previously developed algorithms [8, 10, 11].

Statistical analyses

Overall survival and progression free survival will be estimated using the Kaplan-Meier method. Each member of the cohort accumulated person-years of follow-up from the first drug prescription on the File F Registry until the date of any event (recurrence or death) or until the last update of the Registry Office database.

The effect of potential predictors on survival endpoints will be estimated by a Cox proportional hazards model and expressed as hazard ratio (HR). HRs will be estimated mutually adjusting for available factors or for their combination (e.g. by using the propensity score approach). To investigate the impact of unmeasured features of patients, such as clinical (e.g. severity of hypertension and general clinical profile), antropometric (e.g. body mass index) and life-style (e.g. smoking habit) factors, we will use various approaches to sensitivity analyses, as described below: (1) identifying the strength of residual confounding that would be necessary to explain an observed drug-outcome association; (2) external adjustment given additional information on single binary confounders from survey data using algebraic solutions and a Monte Carlo sampling procedure (Monte Carlo Sensitivity Analysis); (3) external adjustment considering the joint distribution of multiple confounders from external sources of information (propensity score calibration); (4) inclusion of variables strongly related to

the exposure, but unrelated to the outcome (Instrumental Variables); (5) using emergent designs (case-only designs) [16, 17, 21, 22].

Particular attention will be given to the definition of comparable groups of control for each therapy under study, taking into account the design of the planned study (eg. matching, selection of controls, etc.).

IMPACT AND STUDY IMPLICATIONS

The project will provide a detailed description of the use of novel high cost anticancer therapies in clinical practice in the Lombardy Region, which includes 9.5 million inhabitants. In fact, monitoring clinical practice is a necessary first step to increase our understanding of what the appropriateness ratings mean, and to engage in a more meaningful discussion with physicians and patients about their own care.

It will identify the licensed and off-label use of these drug, and evaluate the adherence to the regulatory approval indications. Moreover, the project will provide relevant information on (serious) adverse drug reactions and on overall and disease free survival in clinical practice, whereas, at present, data are available from clinical trials only. This will allow to contribute to effectiveness evaluation, particularly in subgroups of patients under-represented in clinical trials (e.g. older patients, patients with comorbidities). We are in the condition to investigate outcomes in regimens for which clinical trial data are not available (e.g. trastuzumab treatment for metastatic disease in women previously treated with trastuzumab for early breast cancer). We can also use innovative methods (i.e. Monte Carlo Sensitivity Analysis, etc.) to compare different regimens. This project will also allow evaluating strengths and limitations of administrative databases in various aspects of pharmacoepidemiology.

In conclusion, this study will provide relevant information both at clinical and regulatory level about these novel anticancer drugs, which will help clinicians and regulatory agencies in their choices.

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