Lung Cancer 108 (2017) 134–139

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Economic burden of clinical trials in lung cancer in a German Comprehensive Cancer Center

F. Kron[a,b,1], A. Kostenko[a,b,1], M. Scheffler[a,b], D. Müller[c], J.-P. Glossmann[a,b], R. Fischer[a,b], S. Michels[a,b], L. Nogova[a,b], M. Hallek[a], T. Zander[a], J. Wolf[a,b,*]

[a] Department I of Internal Medicine, Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany
[b] Lung Cancer Group Cologne (LCGC) and Network Genomic Medicine (NGM) Lung Cancer, Germany
[c] Institute of Health Economics and Clinical Epidemiology, University of Cologne, Germany

ARTICLE INFO

Article history:
Received 27 January 2017
Received in revised form 23 March 2017
Accepted 28 March 2017

Keywords:
Lung cancer
Clinical trials
Individualized therapy
Precision medicine
Cost calculation
Cancer center

ABSTRACT

Objectives: The recent success of individualized lung cancer therapy has triggered fundamental changes in clinical research strategies. To date there is a strong focus on early proof of concept trials in genetically preselected small patient subgroups. This analysis focuses on the economic burden caused by such trials for advanced lung cancer patients in a German Comprehensive Cancer Center (CCC).
Methods: The profit margins between recruiting groups with ≤3 and >3 patients were compared. Clinical and economic data from clinical trials for advanced lung cancer (LC), pharma-sponsored trials (PhST) as well as investigator initiated trials (IIT), conducted between 2011 and 2015 at the Center for Integrated Oncology (CIO) Cologne, were analyzed using a profit-center calculation model.
Results: 161 patients were enrolled in 27 clinical trials. The key economic parameter determining costs and payments was the 'trial visits'. In comparison of the two groups (A ≤ 3; B > 3 patients enrolled) we found negative profit margins for the low recruiting group (€ −1444). Concerning the number of visits significant differences were found between PhST and IIT ($p = 0.009$). Additionally, sub-analysis show structural differences in cost composition by conducting PhST and IIT.
Conclusion: Trials with low patient numbers and IIT, do not cover the cost. To ensure adequate, cost-covering compensation by pharmaceutical companies CCCs have to thoroughly calculate the cost of early proof of concept trials. The findings of this study also underline the need for novel structures in public funding for investigator-initiated clinical trials in precision medicine.

1. Introduction

The economic impact of lung cancer (LC) is a major challenge for every health system and organization. Driven by rapid progress in oncology and demographic change, cost of cancer care increases continuously. The US spend about $13.4 billion (€12.4 billion) annually on LC (10% of all national expenditures of cancer care) [1–4]. In the European Union (EU) LC has the highest overall cost with €18.8 billion ($20.4 billion) of overall cancer costs including €9.9 billion ($10.7 billion) productivity losses related to mortality [5]. From 2002 to 2008 the LC costs increased from €0.9 billion to €1.5 billion in Germany, reflecting an annually mean increase of more than 8% of care-related (direct) costs [6].

While costs increase, the prognosis of advanced LC (UICC stage IIIB/IV) remains desastrous with a 5-year survival rate of below 5% due to lack of effective treatment strategies [7,8]. Genomic medicine has enabled the development of individualized therapies directed against so called driver mutations, in particular for the treatment of lung adenocarcinoma with a substantial higher efficacy compared to chemotherapy [9]. The further development of such therapeutic approaches combined with state-of-the art molecular diagnostics and phase I trial units requires highly specialized academic centers such as Comprehensive Cancer Centers (CCC). CCC in Germany are predominantly paid by society through statutory health funds and federal research funding. Therefore, these institutions have a high responsibility for cost-effective management of the centers.

In view of the recent dynamics in systemic therapy of LC there is a major need to focus on the hospital management perspective

* Corresponding author at: Department I of Internal Medicine, University Hospital of Cologne, Kerpener Str. 62, Cologne, 50937, Germany.
E-mail address: juergen.wolf@uk-koeln.de (J. Wolf).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.lungcan.2017.03.018
0169-5002/

to evaluate the economic burden from an organizational perspective. Several publications have evaluated the financial impact of oncology trials [10–15]. Emanuel et al. underline the time and cost consuming aspects of providing treatment within clinical trials while Bennett et al. report only a moderate increase in costs compared with standard treatment. In non-small cell lung cancer (NSCLC) several pharmacoeconomic analyses evaluate the cost-effectiveness of chemotherapy strategies and/or best supportive care. However, none of these analyses evaluated the cost-effectiveness of individualized therapy. In addition, these analyses report from different perspectives such as health care payer, insurance or from societal perspective [1,16–19].

Our analysis focuses on economic aspects from a single center perspective of a German CCC in order to identify economic risks and chances in the clinical trial setting.

2. Patients and methods

2.1. Study population and clinical trials

In this retrospective study we analyzed 154 patients with advanced LC (stage IIIB/IV LC) enrolled in one or two of 27 clinical trials (5 IIT and 22 PhST) between 2011 and 2015 (see supplement for further details) at the Center for Integrated Oncology, Cologne (CIO).

The cutoff for visits and duration of patients' treatment was 24th of August 2015. Trial patients prior to 2011 with regular end of treatment (EOT) visit or unexpected study discontinuation were excluded from this analysis. Almost all analyzed clinical trials (26/27) were supported by pharmaceutical companies. Four IIT were funded by fixed budgets according to the total patients' number and recruitment progress (milestone-based payments). One IIT was funded within a public joint research proposal by the Federal Ministry for Education and Research (BMBF). All IIT trial protocols were designed by the Lung Cancer Group Cologne (sponsor University of Cologne). PhST budgets were calculated per trial visit, set up fees and diagnostic costs (e.g. pathology, imaging) were paid in addition

2.2. Economic and statistical methods

Based on the clinical information system of the University hospital of Cologne (UHC) and the clinical trial contracts, we merged protocol related patient data with visit payments. Overhead costs such as administrative tasks prior to initiation-visits and start of enrollment were defined as 'set up fees'. We calculated accrual personnel costs with regard to the annual salaries for public employees and medical duties at university hospitals. This first cost calculation was limited to the requirements of trial protocols excluding standard of care (SOC) procedures. SOC services are provided independently of trial participation and are paid by the health funds. Drug costs were not included since study medication was supplied free of charge in all clinical trials. Costs for independent ethics committees (IEC), legal authorities, statistical analysis or clinical research organizations (CRO) were calculated as 'other costs'. All trial-related cost compositions are combined within total trial budgets with respect to structural budget differences dependent on the PhST or IIT requirements.

In order to compare both types of clinical trials, PhST and IIT budgets were matched by transforming IIT budget milestones into visit-related payments per patient (PP). Set up fees were paid after site initiation, independent of visits and patients' recruitment (only for the PhST). The trial-related costs were divided into: i) staff costs (principal-, sub-investigator (including of protocol writing efforts in IIT), study nurse, coordinator, controller, quality manager and internal assistance, ii) diagnostic costs (e.g. imaging and pathology) and iii) other (pass-through) costs including IEC, legal authorities, statistical analysis or CRO and external management tasks in IIT. Trial-related margins were calculated by comparing total payments to the internal trial costs.

Table 1
Patient characteristics.

Total number of patients	154
Gender (male/female)	59.7%/40.3%;
Age at trial inclusion (yr, mean ± SD)	60 ± 11.5
NSCLC histology	150 (97.4%)
SCLC histology	4 (2.6%)
No. of patients enrolled(all stage IIIB/IV)	161
Patients in phase I/II	148 (91.9%)
Patients in phase III	13 (8.1%)

NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer.

Staff costs per visit (PV) were calculated based on the total annual personnel CTU costs (e.g. principal and sub investigator, study nurses and coordinators, quality manager). To calculate the total amount for the period of 4.5 years we assumed that 10% of these costs are fixed and incur for not patient-related procedures (e.g. set up site preparation and trial administration, ethics submission). Thus, 90% of accrual staff costs are variable costs that incur according to patient-related procedures during trial visits. These costs depend on the number of patients enrolled and number of trial visits. For the calculation of visit-based staff costs for PhST and IIT the fixed personnel costs were extracted. These 10% of the total staff costs (fixed) were then compared to the set up payments only.

Due to internal results of long-experienced documentation of accrual personnel time for PhST and IIT visits from different clinical trials we assumed that IIT visits are 1/3 less time- and cost-consuming as compared to PhST visits. Total visit costs were calculated by multiplying average trial costs by the number of visits.

According to the differences in the budget structure (visit-based payments in PhST vs. fixed milestones and lack of set up fees in IIT) in our subanalysis we subsequently focused on the PhST.

Based on the median enrollment rate of three patients per PhST trial (mean value: 4.3) and long experience in clinical trials in small subgroups, we assumed a cutoff of three patient enrollment to compare group A (trials with less or equal three enrolled patients) with group B (trials with more than three patients enrolled). In both groups, the CTU-based cost- and payment structure was built up by variable (visit) and fixed (set up) components.

IBM SPSS statistics software (IBM Corp., Armonk, NY, USA) for statistical analysis. Non-parametric Mann-Whitney test was applied to test statistical significance of trial visits, treatment duration and profit margins. All costs in this study are provided in Euro. The exchange rate ($/€) was 1 Euro = 10.796 US-Dollars.

3. Results

3.1. Cost–payment analysis of the trials and visits

In a period of 4.5 years we assessed 150 NSCLC and 4 SCLC patients (Table 1). At the time of recruitment, all 161 trial patients (seven patients were enrolled in two different trials) had stage IIIB/IV. 95 patients were enrolled in 22 PhST and 66 patients in five IIT (Table 2). In 27 clinical trials, we observed 2173 trial visits (PhST: 1319; IIT: 854). We identified the trial visit being the key economic factor determining costs and payments in clinical trials. Step-down calculation of the milestone payments relative to the number of patients and the total number of visits PP was provided for IIT. Mean staff payments per visit in PhST were almost twice as high as in IIT. While mean CTU staff costs per visits in PhST were about €200 higher than in IIT with a positive profit margin of €31