RESEARCH ARTICLE

Pharmacophore Development for Anti-Lung Cancer Drugs

Muhammad Haseeb*, Shahid Hussain

Abstract

Lung cancer is one particular type of cancer that is deadly and relatively common than any other. Treatment is with chemotherapy, radiation therapy and surgery depending on the type and stage of the disease. Focusing on drugs used for chemotherapy and their associated side effects, there is a need to design and develop new anti-lung cancer drugs with minimal side effects and improved efficacy. The pharmacophore model appears to be a very helpful tool serving in the designing and development of new lead compounds. In this paper, pharmacophore analysis of 10 novel anti-lung cancer compounds was validated for the first time. Using LigandScout the pharmacophore features were predicted and 3D pharmacophores were extracted via VMD software. A training set data was collected from literature and the proposed model was applied to the training set whereby validating and verifying similar activity as that of the most active compounds was achieved. Therefore pharmacophore develoipment could be recommended for further studies.

Keywords: Pharmacophore - anti-lung cancer drugs - computer aided drug designing - ligand scout - VMD

Asian Pac J Cancer Prev, **16 (18)**, 8307-8311

Introduction

Lung cancer is known to have a high fatality rate among males and females and takes more lives each year as compared to colon, prostate, ovarian and breast cancers (Thomas et al., 2005). Lung cancer is classified into two main types namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) of which NSCLC accounts for about 80% cases and SCLC accounts for 10-15% among all other types of lung cancers (Molina et al., 2008). Genetic factors play an important role in development of lung cancer (He et al., 2012). the GSTT1null polymorphism to be associated with smoking-induced lung cancer and the GSTM1null polymorphism to have a link with non-smoking related lung cancer (Shukla et al., 2013). The early prediction of lung cancer play a pivotal role in the diagnosis process and for an effective preventive strategy (Ahmed et al., 2013).

Non-small cell lung cancer (NSCLC) is a worldwide leading cause of death (Ginsberg et al., 1997). The surgical resections are not applicable when first diagnosed as NSCLC is usually in an advanced stage. The patient may have a possibility of prolonging survival with chemotherapy [Non-small Cell Lung Cancer Collaborative Group]. Chemotherapy for advanced NSCLC is often considered excessively toxic. High and medium levels of physical activity have a beneficial effect on lung cancer by reducing the overall risk of tumor development among both men and women (Sun et al., 2012).

Drugs developed for cancer are single agents although for the maximum advantage they need to be used in recipe with other drugs or therapeutic agents. Initial candidate chemicals or "leads", are often recognized and tested for single agents that change cancer-cell proliferation or prolong survival. This led to the identification of most of the clinically active cancer drugs used today. Specific leads then must be further optimized and assessed to characterize their pharmacokinetic and pharmacodynamic properties and evident toxic effects. Clinical evaluation is performed by trails in humans to identify a maximum tolerated dose, define severe toxic effects, and estimate bioactivity. These trails are time consuming and expensive (Ramaswamy et al., 2007). This meta-analysis provides new evidence supporting the conclusion that residential exposure to radon can significantly increase the risk of lung cancer in a dose-response manner. Drug resistance, especially multi-drug, is the most important cause of failure of small cell lung cancer chemotherapy (Chen et al., 2012)

Pharmacophore is the initial step towards understanding the interaction between a receptor and a ligand. Pharmacophore was often postulated as the "essence" of the structure-activity knowledge they had gained (Gund, 2007). Today's researcher task is to interpret the binding of anatomically varied molecules at a common receptor site. To generate common feature pharmacophore from the set of compounds active for certain receptor, the characteristics necessary for binding receptor in a generalized way (Omoshile, 2000). Understanding of the common binding group properties is vital for determination of the type of inhibitor binding. Pharmacophore model is very convenient for attaining this goal.

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Surface of the cell are the regions where the ligand-receptor and receptor-receptor interaction occur. The process undergo Sequential levels of activity starts initially from the cell surface and then moves towards the intracellular signaling pathways, then gene transcription which corresponds to cellular responses. Epidermal growth factor receptor (EGFR) was initially identified as an abnormally activated or mutated form which leads to a number of other abnormalities in the signaling pathway and hence leads to the formation of tumor (Mendelsohn et al., 2000).

In our research, a 3D pharmacophore model was developed in order to promote the discovery of precise and effective EGFR inhibitor for the treatment of non-small cell lung cancer. The compounds used in this study have been characterized as reported in reference papers. In order to correlate experimental and computational studies we used their bioactivity data.

Materials and Methods

The work was initiated using LigandScout software. LigandScout is a tool for deriving the 3D from structural data of ligand complexes more speedily and evidently in a completely automated and expedient way. It offers flawless workflow both from ligand and structure based pharmacophore modeling (10). LigandScout is thought to be an essential software tool for structure based drug designing, it is not only beneficial for carrying out analysis of binding sites but also for alignment based on pharmacophore and the designing of shared feature pharmacophores. LigandScout runs freely on all common operating systems. Till date a number of successful application examples have been carried out and stand published (Wolber et al., 2005).

The very important and the very first step in pharmacophore model generation is the selection of data set compounds. A number of drugs have been reported that are in some way related to, or used in the treatment of Non-Small Cell Lung Cancer which include Platinol (generic name, cisplatin) (Helsing etal., 1998),carboplatin, Taxotere(generic name, docetaxel), Gemzar(generic name, gemcitabine), Taxol (generic name, paclitaxel), Almita (generic name, pemetrexed), Avastin(generic name, Bevacizumab), Xalkori(generic name, Crizotinib), Navelbine(generic name, vinorelbine , Iressa(generic name, Gefitinib) and Terceva (generic name, Erlotinib) (Lynch et al., 2004; Curran et al., 2011).

The two dimensional (2D) chemical structures of the compounds were drawn using ChemDraw Ultra (8.0) and the structures were saved as. Pdb files. Subsequently the 2D structures as shown below (Figure 1) in the form of Pdb files were imported into LigandScout and converted into corresponding 3D pharmacophore structures.

The pharmacophoric features include H-bond donor, H-bond acceptor, Hydrophobic, aromatic, positively and negatively ionizable groups, the pharmacophore for each compound was generated and the distances among the pharmacophoric features were calculated using VMD software. VMD is designed not only for modeling, visualization, and analysis of biological systems such as proteins, nucleic acids, lipid bilayer assemblies but it may also be used to view more general molecules, as VMD can read standard Protein Data Bank (PDB) files and display the contained structure with their features. A number of application examples have been published to date (Huang et al., 2012). Once the pharmacophore of all the compounds were identified, the ligand was then super imposed so the pharmacophore elements overlap and a common template i-e the pharmacophore model is identified. The training set consisting of four compounds was collected from literature and it was found that the groups show enhanced and similar activity as that of the most active compounds based on the 3D pharmacophore being generated for non small lung cancer.

Results

Pharmacophore analysis is considered as a fundamental part of drug design. The pharmacophore generated by

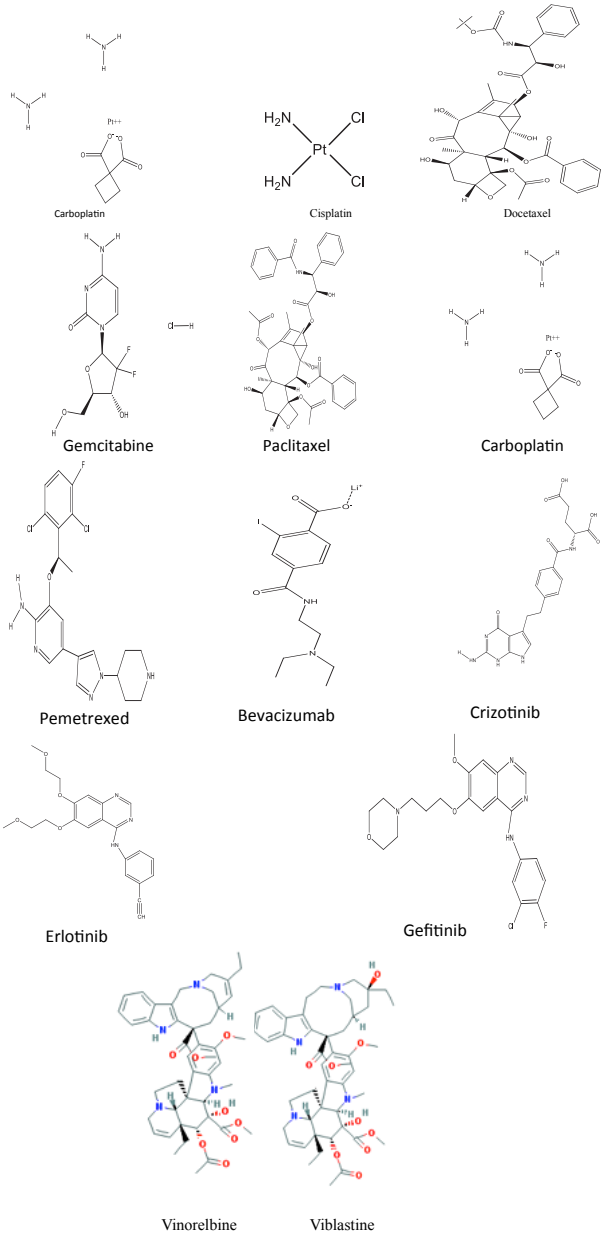

Figure 1. 2D Structures of Selected Data Set of Anti Non Small Lung Cancer

LigandScout for the selected data set of anti non small cell lung cancer showed three main features i-e H-bond acceptor(blue vectors), H-bond donor(blue vectors) and aromatic rings (yellow spheres). The representative pharacophores of each compound are shown in (Figure 2,3,4 and 5). The pharmacophoric features for each compound on the whole are shown in (Table 1). The pharmacophores of all the compounds were then matched and a unique pharmacophore was identified after a detailed analysis. On the whole, the representative pharmacophoric features for each compound are shown in (Table 2). Resembling features were identified after analyzing the pharmacophore of all compounds generated by LigandScout. Then the similar features of all the compounds were superimposed and merged into single pharmacophore. The uniquely identified pharmacophoric features are shown in (Table 3).

Our common featured pharmacophore predicted for three compound of anti non small lung cancer is based

Figure 2. A pharmacophore of Pemetrexed (Alimta®)

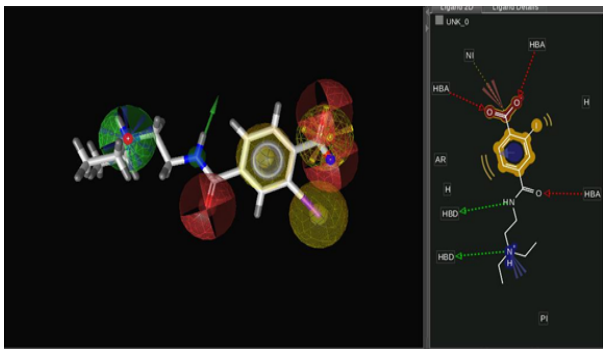

Figure 3. A Pharmacophore of Bevacizumab

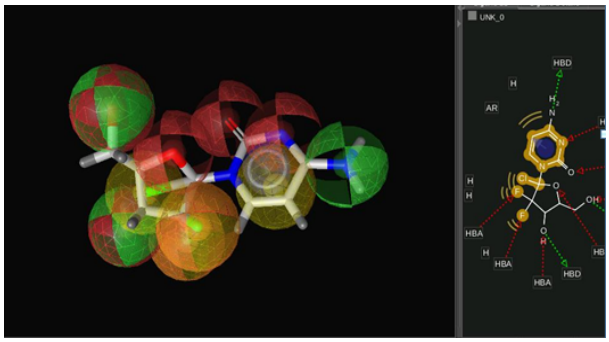

Figure 4. A Pharmacophore of Gemcitabine (Gemzar®)

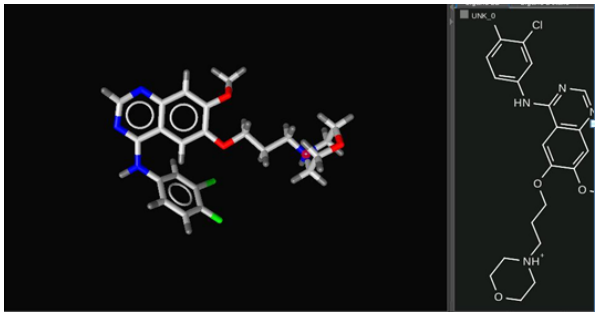

Figure 5. A Pharmacophore of Gefitinib

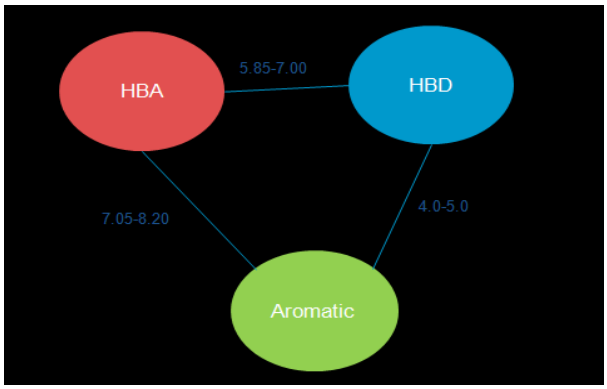

Figure 6. Distance Ranges among Pharmacophoric Features in Predicted Pharmacophore

Table 1. Pharmacophoric Features of Each Compound

Compounds	H-Bond Donor	H-Bond Acceptor	Aromatic Centre
Paclitaxel	+	+	+
Pemetrexed	+	+	+
Bevacizumab	+	+	+
Carboplatin	+	+	+
Crizotinib	+	+	+
Erlotinib Hydrocholride	+	+	+
Gefitinib	+	+	+
Gemcitabine	+	+	+
Methotrexate	+	+	+

Table 2. Pharmacophoric Features of Each Compound

Compound	H-Bond Donor	H-Bond Acceptor	Aromatic Centre
Paclitaxel	4	6	2
Pemetrexed	3	6	3
Bevacizumab	2	3	1
Carboplatin	0	3	0
Crizotinib	2	4	3
Erlotinib Hydrocholride	2	6	3
Gefitinib	2	6	4

Table 3. Uniquely Identified Pharmacophoric Features of Compounds

Compound	H-Bond Donor	H-Bond Acceptor	Aromatic Centre
Bevacizumab	2	3	1
Pemetrexed	3	6	3
Gefitinib	2	6	4

Table 4. Pharmacophoric Triangle Distances of Each Uniquely Identified Compounds

Compounds	Acceptor To Aromatic Ring	Aromatic Ring To Donor	Donor To Acceptor
Gefitinib	7.1	4.76	6.97
Pemetrexed	7.03	4.15	5.85
Bevacizumab	8.14	4.29	6.36

Table 5. The Distance Triangle for Compounds of the Training Set

Model	Acceptor To Aromatic Ring	Aromatic Ring To Donor	Donor To Acceptor
MMDA	5.99	5.52	5.95
Flavopiridol	7.01	4.04, 4	6.18
MethyNonanoate	4.01	7.6	2.24

Table 6. The 3D Pharmacophoric Distance Triangle of the Training Set and the Standard Drugs Respectively

Model	Standard Drugs	Training Set
Acceptor To Aromatic Ring	7.37-8.84	7.01-8.96
Aromatic Ring To Donor	4.39-4.89	4.04-4.62
Donor To Acceptor	6.18-6.97	6.18-6.64

on three HBAs, six HBDs and four aromatic centers. The distance triangle measured between the common pharmacophore features of each compound using VMD is shown in Table 4.The distance ranges from minimum to maximum and have measured between the HBA and HBD,HBA and aromatic ring and HBD and aromatic ring.

The distances among the common pharmacophoric features between the predicted pharmacophore are shown in Figure 6. The distances between aromatic ring and HBD range from 4.15-4.80, between aromatic rings to HBA range from 7.03-8.66 and between HBA to HBD range from 5.85-6.97.

A training set of three compounds was collected from literature i-e MethyNonanoate, MMDA, Flavopirido (Bose et al., 2012). The generated 3D pharmacophore model was applied to the training set whereby validating and verifying their enhanced and similar activity as that of the standard compounds shown in (Table 5). This further confirmed our observation and proposals for a pharmacophore model as it corresponds to the predicted pharmacophore. To support the suggested pharmacophore model, distance was estimated. The predicted distance of the training set and the standard drugs respectively are shown in (Table 6). This table shows the close resemblance of Flavopiridol with that of standard drugs whereby validating that the compound shows high correlation with the predicted pharmacophoric triangle hence having similar activity.

Discussion

The pharmacophore model is a very handy tool for new lead compounds discovery and development. In this study pharmacophore models were built for novel drugs of non small lung cancer, pharmacophoric features were predicted and 3D pharmacophore has been generated for non small lung cancer. A triangle of three different classes has been selected for pharmacophore and Hydrogen bond Acceptor, Hydrogen bond Donor and Hydrophobic character of standard drugs have been filtered out as key pharmacophoric feature. The generated model was applied to the training set and it has been validated and proposed that Flavopiridol shows similar enhanced activity as that of standard drugs, hence could be used for further studies. Moreover Pharmachopore based docking will be used for virtual screening and designing of some novel drugs for non small lung cancer in continuation of this work.

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