

Research, evidence, and ethics: new technology or grey medicine

Haoran Zhai, Wenzhao Zhong, Yilong Wu

Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou 510080, China

Correspondence to: Wenzhao Zhong. Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou 510080, China. Email: 13609777314@163.com.

Abstract: Major pioneering advances of medicine in history tend to manifest in two directions that seem divergent but actually unified with dialectics: one is the important biological principle revealed by in-depth studies from the clinic to the laboratory based on individual cases; the other is the colonial generality displayed by epidemiologic data from large-scale samples. Although advances predominated, we human beings were paying dearly for it due to serious incidents of endangering ourselves and defects of restrictions of laws and ethics. Subsequently, the Nuremberg Code, Declaration of Helsinki and Belmont Report came into light and constrained human experiments and clinical trials. However, the development of such laws and regulations in China is lagging behind and renders China as a breeding ground for gray medicine. There are three lessons we can learn from painful histories and apply to individualized treatment of lung cancer. Firstly, the abuse of Avastin beyond its indications reflected the similar situation of tyrosine kinase inhibitors in lung cancer due to different molecular types and stages of tumors; secondly, the black market of stem cell therapy in China reminds us how to identify the boundaries of clinical trials and clinical treatment, in similar to the cellular immunotherapy of tumors; thirdly, the theory of Xiao's Reflex Arc emerged us to rethink the level of the validity of clinical evidences, which can provide hints related to video-assisted thoracoscopic surgeries (VATSs). In conclusion, clinical applications of new techniques and treatment regimens should follow three points: identify indications and contraindications clearly, obtain informed consent and permission of patients and supervise effectively according to laws and ethics.

Keywords: Clinical research; ethics; lung cancer; modern medicine

Submitted Oct 15, 2014. Accepted for publication Nov 22, 2014.

doi: 10.3978/j.issn.2305-5839.2015.01.01

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2015.01.01>

In 2012, *the New England Journal of Medicine* celebrated its 200th anniversary by publishing a special issue which summarized the development and innovations of modern medicine despite setbacks (1). The major pioneering advances in history tend to display an important biological principle that revealed in-depth studies of individual cases from the clinic to laboratory, which seems divergent, but lead in one direction. For example, the use of diethyl ether in surgery for the first time marked a major breakthrough in anesthesiology, and carrying out an ASD neoplasty for a girl under extracorporeal circulation, which broke the traditional idea that cardiac surgery is a desecration to the art of thoracic surgery. Moreover, the individual case report involving the acquired drug resistant T790M mutation of EGFR-TKI contributed to the research and development of AZD9291, a 3rd generation of TKI-

targeted drugs. In addition, these advances are based on group generalities displayed by epidemiologic data of large-scale samples. Breast cancer surgery, with a history encompassing 2,000 years, developed through five stages (local excision, radical mastectomy, extended radical mastectomy, modified radical mastectomy, and breast-conserving surgery), shows a tendency towards excision extension from small-to-large, then back to small again. Lung cancer surgery, which followed breast surgery, developed through pneumonectomy featuring total hilus ligation, lingering between partial lobectomy and lobectomy to the present standard anatomic lobectomy plus systemic intrathoracic lymphadenectomy, then to selected partial lobectomy and lymphadenectomy over 120 years. The four stages of lung cancer surgery showed a tendency towards excision extension from large-to-small, from small-to-large, then

small again. More attention has been paid to tumor biology in oncologic surgery instead of a blind larger excision extension. Thalidomide was first approved to treat morning sickness in gravidas, but was banned due to congenital malformations (phocomelia); unexpectedly, thalidomide has been shown to be effective in the treatment of multiple myeloma by translational research in recent years. Since 2000, thanks to the standardization of the evidence-based medicine and RCTs, the individualized treatment concept has developed rapidly in various fields, which has provided more high-level evidence, such as the IPASS/OPTIMAL study, which is a milestone in individualized treatment of lung cancer.

The more medical progress that is made, the higher the price paid. Vicious events that involved endangering ourselves and others in the name of science can be found throughout history; initially, scientists only used prisoners and slaves in human experiments, but eventually extended experiments to innocent patients, and even themselves and their family members. Given the fact that there was no rigid restriction regarding experimentation based on laws and ethics, the researchers focused on laws and deliberately carried out experiments of that kind. After World War II, with the trials of Nazis the by World Court and the revelation of a series of syphilis tests on African Americans, the stress from public opinion, as well as a high demand for clinical evidence, contributed jointly to the introduction of a series of criteria, like the Nuremberg Code, Declaration of Helsinki and Belmont Report, which became a “Code of Hammurabi” for constraining human experiments and clinical research. By contrast, the development and popularization of ethics and regulations for clinical research in China is lagging behind, which renders China a breeding ground for gray medicine. A large number of “new techniques” have emerged in China, which have been pursued with reckless abandon. Many new phrases are in common use by patients, such as bone-breaking, leg-lengthening, artificial heart implantation, rehabilitation after brain surgery, and transsexual surgery, many of which are still under exploration in foreign countries or in different phases of animal experiments and clinical research, but unexpectedly carried out in clinical practice in China on a large scale. In the gray zone of supervision, researchers take advantage of patient mindset because they are in such a hurry to see a physician that they fail to recognize fraudulent information online, and confuse the boundaries of medical treatment and clinical research. Without full consent from patients and support from convincing data of

phase III clinical trials, domestic researchers apply clinical studies to clinical treatment with deceptive information. Because China permits research-based treatment without monitoring, in 2009 journals such as *the Lancet* (2) and *Nature* (3) commented on China conducting a large number of controversial treatments, expressing doubt and concerns about the safety, lack of profiles of the early stage trials, and clinical validation.

So, what can we learn from the painful lessons against the backdrop that many domestic regulations remain to be improved? What significance does it bring to the multi-disciplinary comprehensive treatment and accurately individualize treatment in lung cancer? Next, we will list three typical cases, introducing similar controversial problems in the process of standardized management of lung cancer, and further discuss the ties among clinical research, evidence, and ethics.

The first case, in which Avastin was used beyond its indications, became known as the “ophthalmic medication scandal”. Avastin, an anti-angiogenic drug for colorectal cancer, was injected intravitreally in patients with macular degeneration by ophthalmologists in September 2010, which caused a controversy after 55 patients were reported to have intraocular infections. Avastin prescribing information and related ophthalmic clinical guidelines did not address this kind of application, which also has limited representation in the literature. In addition, pharmaceutical companies refuse to legalize the indication for a variety of reasons. Thus, it is illegal when physicians use this drug for non-indications. Avastin has similar pharmacodynamics as lucentis, a drug used in eye diseases and produced by Genetec, which is a different form and up to ten times more expensive. Almost every physician prescribes or recommends Avastin in the treatment of macular degeneration. Although physicians applied the drug beyond its indications in the hope of relieving patient pain and lowering their financial burden, they should be investigated for legal responsibility due to the absence of relevant clinical research, informed consent, and ethics approval. This accident brought drug abuse beyond indications to the spotlight, which also posed a challenge to the clinical workers, i.e., how to harmonize quality, quantity, and degree. The 32nd item of the Declaration of Helsinki emphasizes that patient lives should be the priority, and physicians can adopt medical therapy that has not been tested if no effective therapy exists. Of note, the pre-condition is the absence of standard treatment, the presence of consent and being research-oriented. Similarly, this event precluded many problems existing in

current clinical practice, including the plight of clinicians, patient self-selection, supervision of health administration, overall strategies of pharmaceutical companies, and the role of the Academy of Ophthalmology. Basically, Avastin became a “scapegoat”.

Similarly, “drug-abuse-beyond-indications” events also take place in the vicinity of the tumor. During the last decade, tumor classification has gradually developed from an anatomic to molecular classification. Tumors in different anatomic locations have unique and mutual molecular spectroscopic characteristics; research regarding the same target has shown that different cancers do not develop in the same place. Although the asynchronism can be a great entry point and target for carrying out relevant clinical research, it can also inevitably make drug abuse beyond indications a common phenomenon. For example, in 2014 the third version of the NCCN guidelines for lung cancer (4) added BRAF mutations, a target that was originally studied in melanomas, according to a phase II clinical study of ASCO. In the era of targeted treatment, the conversion from research to guideline has become more rapid. At present, lung cancer features seven targets, including EGFR mutations, ALK, HER2, BRAF, c-MET, ROS1, and RET, each of which has targeted drugs. The applications of each targeted drug are mutually overlapping, which can lead to “super-indication drugs” for untested or unknown targets.

Moreover, different stages of the same cancer may also cause drug abuse beyond indications. For example, TKI has been used clinically for nearly 10 years, although the ESMO guidelines explicitly reject TKI as adjuvant therapy. The NICE guidelines indicate that TKI can be used to direct research, and up to 51% of physicians who took part in the survey still recommend TKI as adjuvant-targeted therapy. A series of clinical studies in this regard have been carried out, and the conclusions on the duration, effect, and benefited populations of TKI adjuvant therapy still remain controversial until today. Based on the recently published BR19 (5), for example, there was no significant difference between the TKI and control groups with respect to overall survival (OS) and progression-free survival (PFS) for the total population and small-sized samples with EGFR mutations, and Iressa has survival curves, even under placebo, which proved that clinical studies cannot be replaced by theoretical speculations. In September 2011, CTONG1104/adjuvant was initiated by CTONG and was inspired by lessons learned from the preceding study design. Of the patients with operable NSCLC and positive EGFR mutations, those with a post-operative

biopsy confirming intrathoracic lymph node metastases (positive N1/N2) were enrolled to receive adjuvant chemotherapy with gefitinib, compared to those with a traditional vinorelbine/cisplatin regimen. The patients with EGFR mutations, R0 margins, and N1-N2 stages were divided randomly to receive four cycles of NVB/cisplatin and 2 years of gefitinib for adjuvant TKI therapy. The end-point target was disease-free survival (DFS), and 220 patients were included in the group 3 years later and followed for 5 years. One of the second end-points was OS after the two groups had been crossed over. The study was conducted for 8 years. The design of the Japanese impact and adjuvant studies was similar, and the two studies were competitive regarding patient inclusion, but the data was shared and analyzed together. Thus far, early TKI adjuvant therapy has been used in clinical studies only, and is not recommended for routine clinical treatment. We are looking forward to the findings of subsequent studies, which are expected to provide high-level evidence for the role of EGFR-TKI in the treatment of NSCLC.

The next case involves the Chinese black market for stem cell therapy, which reflects a basic question with respect to clinical research and treatment. The Belmont Report (6), as an ethical rule and guide for the protection of human subjects, established a boundary between clinical practice and scientific research, and also promulgated the basic ethical rules for studies involving human subjects, which include respecting individuals, benefiting patients, and fair treatment. However, in actual clinical practice, the boundary between scientific research and clinical practice is unclear because studies are often carried out simultaneously. In fact, clinical research and treatment are completely different concepts, and one of the biggest differences is that the subjects in clinical research are highly paid for treatment compensation instead of being charged. According to measures for the management of the clinical application of medical technology, new medical technologies must be subjected to animal experiments and three stages of clinical trials before being utilized in clinical treatment on a large scale and only when the new treatment has been shown to be safe beyond question in terms of safety, efficacy, and medical ethics. Between 2004 and 2008, nearly 5,000 Chinese or English papers that contain the keyword “stem cells” can be retrieved. Approximately 4,000 of the papers involve basic studies, one-half of the 906 papers concerning the clinical application of adult stem cells were written by Chinese researchers. Only 26 Chinese papers and 18 English reports of clinical RCTs are in accordance

with the CONSORT Statement of non-RCTs. A number of Chinese medical institutions tout the remarkable effects of stem cell treatment, but never mention words like “research” or “trial”, in an attempt to avoid supervision from administrative departments in the name of clinical research, and thus charge the high cost of treatment. Although the China Ministry of Health has implemented relevant laws and regulations which establish the category of the third technology, the ethical safety and effectiveness of which remains to be confirmed, the China Ministry of Health failed to prevent the commercialization of stem cell therapy. Currently, patients from all over the world flock to China in pursuit of medical tourism to receive unapproved stem cell therapy, which further promotes the vigorous development of stem cell therapy. These gray medical therapies not only harm the health of patients, but also hinder the healthy and orderly development of these promising new technologies.

Similarly, how adoptive cellular immunotherapy of tumors develops is similar to that of stem cell therapy. There are a variety of factors that make tumor patients accept DC-CIK therapy. First, free online services provide patients with access to relevant immunotherapy information. Patients choose to believe the information, even if fraudulent. It has been said that a paper is like a hospital. Baidu is a contributor to DC-CIK abuse. Google has always asserted innocence, but still fails to drop free online services and advertisements that are profitable, which catalyzes the development, production, and sale of molecular-targeted bulk drugs. Second, high medical expenses encourage low-paid netizens to choose immunotherapy that is covered by health insurance after they are informed with relevant information. Some low-paid netizens, who did not have the chance to take part in clinical research, acquired the non-marketed and inexpensive molecular-targeted bulk drugs through various means, under the guise of “cancer fighters”, according to the level of CEA. Drug abuse with no particular indications causes early drug-resistance, which affects the entire management, treatment, and monitoring of the onset and progression of disease, and even results in patients losing the opportunities of participating in research, and clinical documents lost for unwanted reasons. Tumors progress to chronic diseases, which often require treatment with expensive medications, which burden the patients financially. For example, ipilimumab (7) is a superstar in the field of immunotherapy, and costs 40,000 USD per month for a patient in the US and 15,000 Euros (23,000 USD) per month after the British Department of Health negotiated with the manufacturer. Nevertheless, most patients cannot

sustain ipilimumab treatment. Against this backdrop, are there any laws and regulations that can prevent such situations? In 1948, the UK implemented the National Health Service (NHS), which became the model of a national health insurance system for developed countries. The NHS, featuring a slogan citing “all treatment must be free” may be a dream for Chinese patients. The NHS seems perfect, but is flawed, and gradually exposes problems that cannot be worked out easily, such as, higher and higher medical costs, increasing depletion of medical resources, and more treatment failures and over-treatment, which will probably occur in the next half-century. Against this background, Cochrane, the founder of evidence-based medicine, put forward an eternal idea that all effective treatment must be free. Only “effective” treatment is free, such as targeted therapy based on molecular markers, instead of DC-CIK therapy, which is covered by health insurance. Being scientific is all about effectiveness, so what is effectiveness? Effectiveness is concluded by clinical data that are abundant and persuasive.

In the third case, the theory of Xiao’s Reflex Arc (8) leads us to reflect on whether or not the level of the validity of clinical evidence is up to the standard. The theory of Xiao’s Reflex Arc believes that urination can be controlled by stimulating the skin of the thighs when the somatic nerves that dominate the knee-jerk reflex are connected to the main visceral nerves of the bladder. To prove his design, Xiao has conducted a number of animal experiments; not only did he publish the SCI papers with high scores and win a National Prize for Progress in Science and Technology, but also invited foreign researchers to evaluate his work and build Shenyuan Hospital. Due to a lack of clinical controlled studies, Xiao’s operation remains controversial.

RCTs are the highest level evidence of evidence-based medicine. In contrast to RCTs that compare treatments with two drugs in the system of internal medicine, the specific implementation of surgical RCTs has some inherent difficulties and systemic bias, e.g., the difficulties of group recruiting, learning curves, individualization of surgery, intensive clinical workloads of surgeons, and insufficiency of research funding. Greater than 90% of the surgical literatures consist of case reports or single-center small-sampled retrospective analysis, while multicenter controlled studies of surgical techniques are less visible. Fortunately, video-assisted thoracoscopic surgery (VATS) in the treatment of stage I lung cancer has been widely accepted at present, from which we can learn something when we look back on its development. In 1910, a Sweden physician

observed the intrathoracic status of patients with TB complexed with a pneumothorax through an observation opening with a trocar (9), which was the first report of the application of thoracoscopy. Subsequently, however, the development of thoracoscopy has remained the same for eight decades, and has been used for diagnostic purposes only. It was not until 1992 that Lewis reported intrathoracic surgery under video-assisted thoracoscopy (10), then endoscopic video technology and equipment, and the comprehensive development of other disciplines like two-cavity intubation anesthesia, jointly promoted the progress of VATS, contributing to lobectomy with VATS. Thomas reported 23 cases in which stage I lung cancer was treated with lobectomy under video-assisted thoracoscopy in 1993 (11). The pulmonary vessels were ligated with an EndoGIA 30 V3, a one-time cut stapler which greatly accelerated the process of surgery, and helped surgeons realize that interaction and cooperation with equipment companies can benefit patients. However, conflicts of interest should be avoided since the equipment application is profitable. The development of technology and equipment should be patient-oriented, rather than focusing on whether or not surgeons and equipment companies are making a profit. The development of surgical techniques is often characterized by the accumulation of many miniature improvements. By 1994, McKenna shared the experience of 44 lobectomies under video-assisted thoracoscopy with concomitant lymph node sampling (12), which was a mark of VATS as a basically mature technique in the surgical treatment of lung cancer. At the same time, VATS was also questioned unprecedentedly and faced with challenges from all sides, including whether or not VATS is in agreement with the principle of the original large-incision oncologic surgery, whether or not VATS causes incision planting, how to decide how many lymph nodes should be dissected, how to handle surgical complications, whether or not there is a statistically significant advantages regarding post-operative pain, hospitalization time, and recovery of lung function, and whether or not the prognosis is improved. Faced with increasingly fierce questioning and challenges, McKenna continued the surgery, and accumulated experience with large samples containing thousands of cases with complications, the incision planting rate, and the rate of conversion to thoracotomy (13), thus providing rigorous follow-up data, and VATS videos he recorded, which brought a brand new communication experience online. In 2000, Sugi made an attempt to conduct a prospective RCT of small-sized samples which compared the VATS

group and a traditional incision group (14). Therefore, in contrast to clinical research involving drugs, surgery is a highly individualized discipline, the operative process of which is difficult to standardize. In multicenter studies, the modes of operations differ at different centers; even at the same center, different surgeons have different techniques and experiences. For an individual surgeon, operations differ due to various factors. Over time, the surgeon overcomes the learning curve (15), with the complications of surgery declines as experience accumulates. In 2007, CALGB verified the definition of technical standards of a complete lobectomy under thoracoscopy (16), including visualization of equipment support, two incisions with an approximate diameter of 0.5 cm, avoidance of rib injuries, individual decisions on the order of disconnection of the trachea, arteries, and veins by patients, and standard lymph node sampling. Based on the evaluation of both the number of surgeries by surgeons who took part in the study and the collection of associated videos, CALGB39802 has become an example of the combination of individualization and standardization in surgery. A systematic review consisting of 2 RCTs and 19 non-randomized controlled trials published in 2009 in *JCO* provided the evidence of benefit for stage IA-IB lung cancer treated with VATS on the basis of evidence-based medicine (17). The same year, VATS was first written into the NCCN guidelines, becoming one of the available options for lung resection (18). VATS is a technique which can truly embody the concept of individualized, minimally invasive surgery and achieve transformation and the leap from being technology-based to patient-based. Only when better combined with tumor molecular biological behavior can comprehensive treatment be multi-disciplinary, standardizing the way for selective sub-lobectomy or lymph node sampling under conditions of wall-attaching growth and high concentration of GGO. Domestic researchers have accumulated rich experience in both technology and evidence on VATS (19-22). Exciting achievements on one-way and single-hole resection under 3D thoracoscopy have been made and carrying out contrast study of sub-pulmonary lobe by analyzing and pairing multicenter data.

In conclusion, the vitality of science lies in innovation. The emergence of any new technology and new idea deserves understanding and acceptance of the public, including the 3rd type techniques. Given the fact that there is no sufficient medical evidence, the clinical application of the new technique brings awareness of the following three points: (I) patients should be informed and their permission is needed, as is effective supervision, after all boundaries

between clinical practice and research is standard treatment that is dynamic; (II) abusing drugs beyond indications is just like an accident of wire walking, clinical studies fail when selection of patients is inappropriate, and new technology is an opportunity and challenge; and (III) we need to balance science, commerce, and innovative practice with better supervision and support to promote the benign development of new technology, which plays an irreplaceable role in advances in medicine.

Acknowledgements

Funding: This work was supported by grants from the National Natural Science Foundation of China (81001031, 81372285), grant S2013010016354 from the Natural Science Foundation of Guangdong.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Zhai H, Zhong W, Wu Y. Research, evidence, and ethics: new technology or grey medicine. *Ann Transl Med* 2015;3(2):15. doi: 10.3978/j.issn.2305-5839.2015.01.01