Editorial

Independent Clinical Research May Alleviate Disparities in Cancer Treatment

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ABSTRACT

Disparities in cancer care are a reality of the modern world. Unfortunately, current clinical research is in the hands of for-profit pharmaceutical companies and of researchers from the developed world. Problems specific to cancer care in developing countries and among deprivileged populations are ignored. Independent clinical research can offer new valuable knowledge and identify affordable and cost-effective treatments. As such, research not depending on commercial sponsors should become one of the important avenues to alleviate the problem of cancer disparities.

Key words: Clinical research, disparities in cancer care, cost-effective treatment

There is no doubt about the existence of significant disparities in access to cancer care, both within individual countries and internationally. The deprivileged population within the developed countries and great majority of the population in developing countries have little or no access to programs of cancer prevention, early diagnosis and up-to-date treatment. Disparities are even worse due to poor education and due to widely spread mis-conceptions regarding all issues connected to cancer: Its cause and biology, potential curability, and effectiveness of scientifically-based or traditional treatment.

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The gap between the rich and the poor in access to modern cancer care is widening. This is due to two diverging trends. On one side is global liberal economy which affects traditional local economies, leads to unemployment, increases poverty and imposes increasing pressure on national budgets, including available resources for health care. On the other side are increasing costs for modern medical equipment, for new drugs and for education and employment of health professionals.

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Most of these issues will be dealt by other authors in this volume. My modest contribution to this discussion focuses on the importance of independent clinical research. As we will see, most of clinical research is nowadays in the hands of for-profit pharmaceutical companies. Furthermore, vast majority of investigators come from developed countries. It comes as no surprise that virtually all research is about new, expensive drugs and ignores the problems of limited resources. We will then present examples of clinical research independent from commercial sponsors. Such an approach can lead to valuable new knowledge and offer opportunities for effective low-cost anti-cancer treatment.

My final introductory comment is on choosing thoracic oncology for supporting my discussion. The reader will understand that its is virtually impossible to cover the whole vast area of oncology – from pediatric oncology to brain tumors, lymphomas, cervical cancer and geriatric oncology. Thoracic oncology has been my personal field of interest for the past two decades. While each field of oncology has its specific characteristics, I believe that it is quite appropriate to support our discussion with experience on lung cancer, the first cause of cancer-related death worldwide.

Clinical Research in Thoracic Oncology

In a recent and yet unpublished survey, we analysed clinical trials on treatment of advanced lung cancer. The survey included papers in English language, published between 2013 and 2015 and included in PubMed database. The desciptors were NSCLC and/or SCLC, with the following limitations: Clinical trial; publication between 01/01/2013 and 31/12/2015; humans; English language. The initial search gave 948 publications. This list was then manually reviewed. After excluding review or opinion papers, trials for loco-regional disease (surgery and/or radiotherapy, neoadjuvant, concommittant or adjuvant chemotherapy) and Phase I clinical trials, 349 publications on advanced lung cancer were selected. Sixteen trials were reported more than once, highlighting a different aspect of the same trial. In these cases, information from both publications was merged so as to avoid duplication of the same experience. Our survey over a 3-years period therefore includes reports on 333 trials.

Here are some figures from the survey:

- Total number of patients included in all trials: 75.467
- Median number of patients per trial: 88
- Median % of responses (complete + partial remission), first-line treatment: 40.0%
- Median % of responses (complete + partial remission), second-line treatment: 12.1%
- Median time to progression, first-line treatment: 5.9 months
- Median time to progression, second-line treatment: 3.4 months
- Median overall survival, first-line treatment: 13.4 months
- Median overall survival, second-line treatment: 10.1 months
- Median % of patients with any grade 3 or higher toxicity: 50%
- Proportion of trials which included quality of life among endpoints: 21%
- Financial support: Commercial sponsors: 44.1%; commercial and public support: 17.8%; public support: 13.8; no support or no data: 24.4%.

Clearly, great efforts are being made to find more effective treatments for lung cancer. Nevertheless, figures on proportion of patients who respond to new treatments, on time to progression and on survival remain disappointingly low. At the same time, a substantial proportion of patients suffer from severe toxicity. In an average trial of second-line treatment, a patient has 12% of chances of experiencing an objective response, while his/her likelihood of severe toxicity is at 50%. Finally, patients' well-being is rarely in the center of our attention: Only 21% of trials report offer at least some data on quality of life. This is hardly acceptable, considering that quality of life is of crucial importance for a patient with incurable disease.

Of interest for our discussion is also the country of origin of the principal investigator [Table 1]. Among developing countries, China is clearly an exemption – and it is indeed questionnable whether China with its strong and rapidly expanding economy still belongs to the category of developing countries. For all other developing countries, it is clear that they do not participate in the process of shaping medical research. In case these countries are involved in research, their role is a passive one: their physicians and patients participate in clinical trials designed and sponsored by investigators and companies from the developed part of the globe. Such a sub-ordination clearly leads to a biased design of clinical research: All attention is given to new expensive drugs, while the problems of affordable cost-effective treatment and of proper supportive care are ignored.

Independent Clinical Research: Illusion or a Real Possibility?

During the last six decades, understanding of the cancer biology, diagnostics and treatment have changed dramatically. It is virtually impossible to find a cancer for which the optimal treatment has not changed. Either cure

Table 1: Twenty countries with the largest population: comparison to number of clinical trials for advanced lung cancer, as published between 2013 and 2015

Rank	Country	Population	Percentage of world population	Number of clinical trials
1	China	1,377,155,844	18.79	32
2	India	1,285,890,000	17.5	1
3	USA	323,826,000	4.42	84
4	Indonesia	258,705,000	3.53	0
5	Brazil	206,059,291	2.81	2
6	Pakistan	193,968,424	2.65	0
7	Nigeria	186,988,000	2.55	0
8	Bangladesh	160,908,496	2.2	0
9	Russia	146,600,000	2	1
10	Japan	126,960,000	1.73	64
11	Mexico	122,273,473	1.67	1
12	Philippines	103,242,900	1.41	0
13	Ethiopia	92,206,005	1.26	0
14	Vietnam	91,700,000	1.25	0
15	Egypt	91,095,030	1.24	0
16	DR Congo	85,026,000	1.16	0
17	Germany	81,770,900	1.12	15
18	Iran	79,328,200	1.08	0
19	Turkey	78,741,053	1.07	1
20	France	66,689,000	0.91	12

or prolonged survival is now a realistic expectation for the majority of cancer patients.

The basis for significant progress in cancer management is clinical research. Its indispensable components are modern diagnostic procedures, including sophisticated pathological analysis of the tumor and precise imaging techniques to monitor the extent of the disease and its response to treatment. In addition, most of clinical trials include new and expensive drugs.

Due to increasing costs, most of medical research is now sponsored by pharmaceutical companies. Cooperation of the academic community with commercial sponsors is invaluable in exploring new approaches in cancer management. In some instances, pharmaceutical companies design clinical trials and organize their practical implementation; in other cases, companies offer financial support to trials initiated by the researchers. The question is not our attitude towards industry-sponsored clinical trials in oncology; rather, the question is whether there is still room for academic research without financial support.

For many renowned scientists, independent academic research will not lead to new knowledge and is therefore futile. I do not share that view. When facing a therapeutic problem, one can often see treatment modalities which are not commercially interesting: innovative combinations of drugs for which the patent protection has expired, or application of very low doses of drugs.

As a practical example of independent academic research which can lead to significant reduction of costs of anti-cancer treatment, I wish to share with you the experience on treatment with low-dose gemcitabine in prolonged infusion. As we will see, this treatment has remarkable activity against non-small cell lung cancer, mesothelioma and some other tumors. In addition, the treatment has low toxicity and is very cost-effective.

Gemcitabine is one of the key drugs for the treatment of many tumors, including lung cancer, breast cancer and bladder cancer. According to the original prescription, the drug is given in a relatively large dose (1000 – 1250 mg/m^2) in brief, 20-minutes infusion. In its parent form, the drug is inactive: only after entering the circulation, the drug will be converted to its active tri-phosphate form. Since the enzyme responsible for phosphorylation is quickly saturated, rapid infusion of a relatively large dose means that most of the drug will be excreted from the body in its original inactive form. However, a long infusion over 4 to 6 hours leads to a much higher conversion rate: only 250 mg/m^2 (20% of the normal dose) is needed to achieve anti-tumor activity.

A complete survey of clinical trials on low-dose gemcitabine in prolonged infusion is clearly out of scope for this contribution. In a brief summary, this treatment alone or in combination with other drugs is effective against non-small cell lung cancer, mesothelioma and bladder cancer. Hematologic toxicity is very acceptable. However, at variance to gemcitabine in standard high dose which rarely causes alopecia, low-dose gemcitabine often leads to alopecia. This phenomenon may be attributable to a much longer exposure to the drug. Furthermore, it may be that for its anti-tumor effect, duration of exposure to the drug is more important than its peak concentration. This might explain unusually high response rate and clinical benefit in mesothelioma, a notoriously chemo-resistant tumor. A reader interested in this particular treatment will find more information in publications which come from a wide spectrum of countries: Slovenia, India, China, Mexico and Egypt.[1-9]

The relation between median survival and costs of 4-month treatment for mesothelioma is shown on Figure 1. The combination pemetrexed and cisplatin, the one recommended in virtually all modern guidelines, is by far the most expensive. Yet, low-dose gemcitabine in prolonged infusion with cisplatin appears as more effective at only a fraction of costs.

We included the discussion on tratment with low-dose gemcitabine in a volume devoted to disparities in cancer care for two reasons. The first one is that this treatment is very cost-effective and hence affordable also to many patients for whom the costs for western recommendations and schedules are prohibitive. The second one is that all clinical trials quoted in this discussion were completed without any support from pharmaceutical companies. This was confirmed at a recent ASCO meeting in Chicago: none of us who presented experience on treatment with low-dose gemcitabine had received any financial support from the industry.

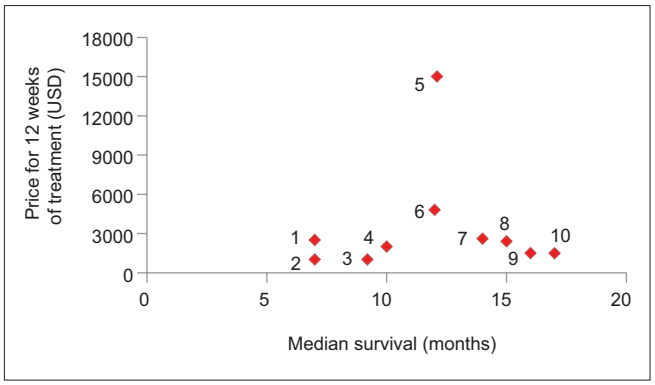

Figure 1: Malignant mesothelioma: relation between reported median survival and costs of individual treatment schedules for 12 weeks of treatment. Costs are based on prices of drugs in European Community for 2015; costs in different parts of the world and/or at different time may vary. Numbers refer to the following drug combinations: 1–irinotecan, cisplatin; 2–mitomycine, vinblastine, cisplatin; 3–cisplatin; 4–doxorubicin, cisplatin; 5–pemetrexed, cisplatin; 6–gemcitabine, cisplatin; 7–doxorubicin, cyclophosphamide, cisplatin; 8–mitomycine, interferon, cisplatin; 9–5-fluorouracil, mitomycine, etoposide, cisplatin; 10–low-dose gemcitabine in prolonged infusion, cisplatin. List of publications is available with the author

Conclusion

Many factors contribute to disparities in cancer care. Their roots can be traced at various levels: Individual, social group, national or even global. It is clear that any single intervention to reduce disparities may bring only limited benefit.

In our discussion, we focused on clinical research, an indispensable and most valuable avenue for progress in care for cancer patients. The benefit of clinical research are obvious and are important for every patient, those with affluent bacground and also those to whom this volume is dedicated. Still, most of global research is now oriented towards new drugs and new treatment, and is invariably linked to rapidly increasing costs. We should not blame pharmaceutical companies which pursue their financial interests. Rather, we urgently need promotion of independent clinical research focused on particular problems specific for the deprivileged population. Clinical research without financial support is feasible and can lead to valuable new knowledge. This may become one of the important avenues to reduce disparities in cancer care.

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Conflicts of interest

There are no conflicts of interest.

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