COMMENTARY

Fight Against Cancer in Countries with Limited Resources: The Post-genomic Era Scenario

Sanjoy Kumar Pal [a], Balraj Mittal [b]

Abstract

   The enormous advances in science and technology in the 20th century have facilitated the process of globalization with the aim of a better quality of life for all. Paradoxically, the gap between the rich and the poor, for both nations and people, is constantly widening. The actual trends in human genome research are leading towards promising genomic medicine, but it will be expensive and inaccessible for many. Also, it may not offer a quick fix 'cure' for various types of cancers. The biggest challenge before the clinicians now is the management of the rising incidence of cancer in developing countries, with little prospect of more resources becoming available to fight the disease. The death rate from cancer in the developing countries is set to rise at least 3-fold by the year 2025 largely due to the increased life expectancy, containment of infectious diseases and changing lifestyles. It is estimated that about 50% of cancers are curable if they are detected early and treated appropriately. Screening has a major role in early diagnosis. However, in the developing world around 80% of cancer patients have late stage incurable disease when they are diagnosed. Moreover, in a developing country like India, about 70% of the population obtain medical help from private practitioners. Nearly half of those who seek medical help utilize alternative and traditional systems of medicine. Appalling poverty, poor hygiene and complex social dynamics, pose major hurdles in this regard. Many in the private sector who call themselves doctors have no medical degree. By 2030 tobacco is expected to kill 10 million people worldwide, out of which 70% of the deaths will occur in the developing countries. Control of usage of tobacco has still not achieved a conducive atmosphere. It is now realized that the research information and knowledge generated in the west may neither be relevant nor applicable to developing countries, due to differences in social and cultural attitudes, lifestyles and lack of sophisticated technologies. Though the sequencing of the human genome will have a major impact on the prevention, diagnosis, treatment, monitoring, and outcome of cancer, the cancer scenario in the developing countries for the next 20 years is likely to be more or less the same, rather than presenting a radically different picture. Cancer awareness and screening programs for early detection thus should be continue to be given utmost attention .

Key Words: Cancer-developing countries-post genomic era

Introduction

   Chronic diseases are the largest cause of death in the world. In 2002, the leading chronic diseases - cardiovascular disease, cancer, chronic respiratory disease, and diabetes caused 29 million deaths worldwide. Despite growing evidence of epidemiological and economic impact, the global response to the problem remains inadequate (Yach et al 2004). The enormous advances in science and technology in the 20th century have facilitated the process of globalization with the aim of a better quality of life for all. Paradoxically, the gap between the rich and the poor, either between nations or persons, is constantly widening. Consequently, the access to health care and education, among other benefits, is becoming more limited for the poor (Cantu 2001). A few developed countries control, or have a dominant influence over, the world's economic, political, and cultural resources (Navarro 2004). The actual trends in human genome research are leading towards a promising genomic medicine, but which will be expensive and inaccessible for many. Since the private funding for R&D have at least double the public ones in the last few years with the consequent bias in focusing on high prevalence disorders in the G 8 countries and neglecting to a certain extent the diseases of the poor.

aDepartments of Gastroenterology and bMedical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow – 226 014 (UP) India Fax No. +91-522-2668017, 2668074   Email: sanjoypal@yahoo.com   balraj@sgpgi.ac.in

Inadequate access to treatment (pharmaceuticals and other modern technology) plays a role in perpetuating this disparity. Drugs and vaccines may not be accessible because of excessive cost or because development of the required products has been neglected (Vainio 2002). The biggest challenge before the clinicians now concerns the management of the rising incidence of cancer in developing countries, with little prospect of more resources becoming available to fight the disease (Pal and Mittal 2004). Over half of the world's cancer burden is carried by the developing world, which has access to limited resources to fight the disease. The death rate from cancer in the developing countries is set to rise at least 3-fold by the year 2025 largely due to the increased life expectancy, containment of infectious diseases and changing lifestyles. To address these problems an initiative better known as Challenge was launched at the XVI International Cancer Congress in New Delhi at the initiation of European School of Oncology (Mittra 1997).

New Medicines Versus Old Approaches

The sequencing of the human genome will have a major impact on the prevention, diagnosis, treatment, monitoring, and outcome of cancer. Progress will most likely occur in a stepwise fashion with the biggest initial impact in diagnosis and molecular targeting of new medicines (Zoon 2004). Advances in genomics and proteomics have already resulted in major findings that are facilitating earlier cancer diagnosis and disease stratification. Someday, it may be possible to use gene-by-gene basis to determine which patient will respond or have adverse response to different anti-cancer drugs, and specifically tailor their therapy (Ratin and Relling 2001). However, of concern is the cost involved in obtaining such information and the tangible benefits (Moore 2001). It is impossible to fully predict the impact of the Human Genome Project on cancer treatment (Ratin and Relling 2001). However, the scenario for the next 20 years is likely to be more or less the same rather than a radically different picture (Cavalli 1999). New diagnostic tools, especially novel pharmacological approaches and molecular bioinformatics will be a major political problem for the developed world where health-care budgets are already tight, but it will have devastating effect in developing countries, which will be the home for most of the 15 million new cases of cancer per year projected for 2020 (Stewart and Kleinues 2003). In developing countries many inexpensive drugs are not readily available and some very expensive drugs are often prescribed for cancer treatment, creates a tremendous financial burden to patients (Rajagopal and Venkateswaran 2003).

Although age-adjusted cancer death rates have started to decline in the United States and other developed nations due to widespread screening programs that detect cancers at early, treatable stages - cancer in developing countries is on the rise (Wilson et al 2004). Ironically, rising life expectancy in those nations along with the adoption of "Western lifestyle" will leave many more people vulnerable to cancer. Unfortunately, the early detection tools and treatment technology that have helped control cancer in wealthier lands are often not readily available in many other countries. Much of this increased cancer burden will take the form of cancers that affect women - not only breast, cervical, and other gynecologic cancers but colorectal cancer, lung cancer, and other malignancies related to tobacco. Cancer of the oral cavity is more prevalent in developing countries, where many people are addicted to tobacco chewing and maintain poor oral hygiene (Das and Nagpal 2002). By 2030 tobacco will kill 10 million people worldwide (Gilmore and Collin 2002). Tobacco industry marketing has played a crucial part in the spread of smoking habits around the world over the past three decades, research has established that tobacco advertisement encourages people to start smoking as well as ensuring that existing do not give up (Anderson et al 2002). Promotional activities, such as merchandising, sports sponsorship, and loyalty schemes, all encourage smoking. Many tobacco producers use sophisticated techniques to target potentially profitable groups, such as young or disadvantaged individuals, but rarely make any compensation for the social consequences of widespread tobacco use. A global tobacco control treaty is now essential because the tobacco industries use of international trade agreement, cigarette smuggling, and global marketing techniques has undermined national control measures and rendered them insufficient to control the tobacco epidemic (Gilmore and Collin 2002). The industry uses various tactics to penetrate new markets outside industrialized countries. As a result the tobacco epidemic has grown in size and gradually shifted its focus from high to low and middle-income countries. By 2030 the proportion of tobacco related deaths occurring in the developing countries will increase from 50% to 70% this shift in disease pattern will add to growing global inequities as the burden of tobacco related disease grow in the South while profits from cigarette sale accrue to companies in the North. Recently, Indian Government has introduced 'The Cigarettes and Other Tobacco Product Act,' which ban smoking in 'public places' and outlaws "sponsorship of sports and cultural events by tobacco companies". Enforcing the new law could actually save India money, since the cost of treating tobacco-related disease, about Rs. 135 billion is more that double the revenue the government receives from the tobacco industry, at around Rs. 55.5 million (Anon 2001a). Unfortunately, 80% of tobacco smoked in India is in the form of bidis, hand rolled cigarettes that are not covered in the Act.

Cancer Prevention

It is estimated that about 50% cancers are curable if they are detected early and treated in appropriate algorithm. Screening has got a major role in early diagnosis (Gangopadhyay and Mallik 2003). However, in the developing world around 80% of cancer patients have late

stage incurable disease when they are diagnosed. Moreover, in a developing country like India, about 70% of the populations obtain medical help from private practitioners. And nearly half of those who seek medical help obtain it from alternative and traditional system of medicine. Appalling poverty, poor hygiene and complex social dynamics, pose major hurdle in treatment (Pal 2002). Many in the private sector who call themselves doctors have no medical degree (Kumar 2004). It is now realized that the research information and knowledge generated in the west is neither relevant nor applicable to developing countries due to the difference in social and cultural attitude, lifestyle and lack of sophisticated technologies (Mittra 1997). About 85% of the world's people live in developing countries – but these countries house only about one third of the world's radiotherapy facilities. There is also huge shortage of specialist in these countries. In this scenario it is emphasized that general practitioners and paramedical staffs should have a greater role to play in cancer detection and management (Gangopadhyay and Mallik 2003).

Physicians specializing in cancer care for women need to be alert to every opportunity to improve cancer screening and prevention among the growing, aging populations of less-developed countries. About 80% of cervical cancers occur in these countries. The vast majority of women in developing countries currently have no options for avoiding this disease, despite the fact that it is highly preventable. The cervical cancer screening programs (CCSP) have not been very efficient in the developing countries. This explains the need to foster changes on policies, standards, quality control mechanisms, evaluation and integration of new screening alternatives. Cervical cancer is a disease most frequently found in poverty-stricken communities and reflecting a problem of equity at both levels gender and regional, and this, is not only due to social and economic development inequalities, but to the infrastructure and human resources necessary for primary care. For this reason, the CCSP program must be restructured, a) to primarily address unprivileged rural and urban areas; b) to foster actions aimed at ensuring extensive coverage as well as a similar quality of that coverage in every region; c) to use screening strategies in keeping with the availability of health care services. In countries with a great regional heterogeneity, a variety of screening procedures must be regulated and standardized, including a combination of assisted visual inspection, cervical cytology and Human Papilloma Virus (HPV) detection; d) regional community intervention must be set up to assess the effectiveness of using HPV detection as an strategy in addition to cervical cytology (pap smear); e) the practice of colposcopy must be regulated to prevent the use of it in healthy women at a population level, thus preventing unnecessary diagnosis and treatment which not only are expensive but also causes unnecessary anxiety to women at risk; f) the operation of those clinical laboratories using HPV as a detection strategy must likewise be accredited and regulated and g) the CCSP program for assuring health care quality should meet the expectations of its beneficiaries, and

increase the knowledge in cervical cancer related matters. Finally, though a variety of clinical tests on prophylactic and therapeutic vaccines against HPV are recently being developed worldwide; it will take at least from 5 to 10-years time to have them available in the market. For this reason, it will be necessary to intensify the CCSP programs (Lazcano-Ponce et al 2003).

The Asian Scenario

In many developing countries, lack of inadequate medical facilities in primary health care sectors, poor infrastructure and information systems constitutes an important barrier to development of comprehensive screening programs and the effective control of cancer. Moreover, lack of financial resources often compels many cancer patients to venture into inexpensive alternative medicines in search of cure and palliation (Pal 2002). The use of complementary and alternative medicine (CAM) is widespread and reflects many needs and concerns that are not being met by conventional medical practice. CAM poses new challenges in modern oncology. Though there is no evidence that alternative medicine is anyway more effective than conventional medicine, but the public opinion and interest about CAM is strong and growing (Vicker and Cassileth 2001). Some forms of CAM viz. acupuncture and hypnosis are now integrated into mainstream medicine in western world for the management of cancer pain. The incidence of cancer increases exponentially with age and a large number of cancer patients are the older members of society. In many developing and some developed countries, the disease is usually detected at a stage when it is too late for aggressive anticancer therapy to have the desired effect. In such situations, CAM has an important role to play in palliative care of patients when cure is no longer the objective. A wide variety of complementary therapies are claimed to relieve stress and increase quality of life by producing relaxation (Pal and Mittal 2003). In India, palliative care is in a relatively early stage of development and consequently faces numerous problems. The extent of problems relating to the lack of such care is not well described for cancer or nonmalignant diseases. The government's palliative care policy has not been implemented. There are clear needs for improvement in multiple areas that must be addressed as new services develop. A system based on outpatient care has proven cost-effective, empowering families to care for patients at home (Rajagopal and Venkateswaran 2003). Most cancer patients suffer moderate to severe pain during the terminal phase of the disease. This pain is unpredictable and produces fear and anxiety in patients and family members. Morphine is the gold standard analgesic to control this pain, but its availability is restricted. The fear of diversion of morphine for non-medical uses has led to severe control on its availability. Studies have shown that diversion of medical morphine is not really an issue. The courts in India have issued directives to improve the availability of the drug, yet majority of Indian patients have very poor access to the drug

(Ghooi and Ghooi 2003). Supportive care to alleviate the symptoms of cancer and its treatment is important for continuation of conventional treatment and greater ailment-free survival. Psychological support, assurance and proper information to patients and family members and forming a healthy network between different levels of medical professionals can form the gateway to combat the disease (Gangopadhyay and Mallik 2003).

In developing countries a large proportion of cancer patients try various herbs for cancer treatment and palliation. Cancer treatment involving herbs is one of the most popular alternative cancer therapy practiced worldwide. Recent evidence suggests that many traditional Chinese medical therapies can be effective for the supportive care of cancer patients (Sagar and Wong 2003). Chinese Fu Zheng herbs have been reported to increase survival when combined with radiotherapy for patients with nasopharyngeal cancer, and when combined with chemotherapy for patient with stomach and liver cancer (Macek 1984; Wang 1990). Herbs have been used to treat cancer since 2828 BC more than 3000 species of herbs used in treating cancer are known to biomedicine. Over hundred plant-derived substances are used as drug globally. Herbal medicine has been the starting point of many important drug discoveries. Vincristine sulfate and vinblastin sulfate used in a variety of malignancies is isolated from herb Catharanthus rosens (L) G. Don or Vinca rosea L. Derivatives from Podophyllum peltatum L are semisynthetic etoposide and teniposide. Gemcitabine is derived from Cryptotheca crypta. Amongst the most significant developments in chemotherapy over the past decade has been the emergence of taxanes and topoisomerease I inhibitors. The origin of these drugs is from nature (Smyth 2001). The recent reports of anticancer compound Ecteinascidin 743 (Et 743) from Carribbean sea squirt (Bonetta 2001), highlights the need of imagination. Acute promyelocytic leukemia (APL) is often curable today through the combined use of trans-retinoic acid and chemotherapy. The disease occurs as a result of the fusion of the APL gene with the retinoic acid receptor alpha-gene. Treatment of APL with retinoic acid preceded the molecular genetic findings. It was part of Chinese folk medicine (Mervis 1996). We learnt something that is hardly new in medicine. Imagination, open-mindedness and keen clinical observations are essential for any discovery. Herbal medicines are likely to play an important role in cancer management in developing countries in the post genomic era. Proper research attention in this area is thus required.

The Rationale for Antitumor Drugs

The rational mind tells us that the relief of human suffering from disease is attainable through a series of logical steps. First, science detects the cause of disease or its pathophysiology followed by interventions to prevent or treat the disease. The basic premise is that disease process should yield to logical thought process. Despite the fact that cancer research have generated a rich complex body of knowledge, and more additions are likely in the post genomic era, but the road from gene to therapy and prevention would be slow and unpredictable (De la Chapelle 2001). Ideally, the detection of a gene whose mutations contribute to cancer should lead to the development of a drug or procedure that cures or prevents that cancer. So far this sequence of events has occurred extremely rarely. A glimmer of hope is provided by the example of chronic myeloid leukemia (CML). Over 40 years ago a specific marker, the Philadelphia chromosome was found. Over 25 years ago the Ph1 was found to be caused by a translocation. Over 10 years ago the translocation was found to lead to the fusion of two genes creating a hyperactive tyrosine kinase. After many years of endeavor with small-molecule compounds, finally STI571 was identified to have the desired effect. Today, after years of clinical trials, STI571 therapy has yielded impressive result for patients in the chronic phase of CML. However, the drug is not effective in the acute phase and long-term treatment (Anon 2001b).

The recent remarkable progress in identifying molecular alteration in human tumor cells has unfortunately not been paralleled in the field of anticancer drug discovery. The shortage of effective anticancer drugs is due in part to the fundamental difficulties associated with the development of any safe effective drug. It remains a formidable task to design small molecules that alter the function of macromolecules with both sensitivity and specificity (for example, an enzyme with a small active site). It is even more difficult to inhibit protein-protein interaction mediated over a large surface, or to restore function to a defective protein. Many of the genetic alteration frequently found in tumors are loss-of-function, mutation in tumor suppressor genes and thus do not constitute ideal drug targets, because it is difficult to develop drugs that restore the function of a missing or altered protein (Hartwell 1997). The BRCA 1 and BRCA 2 genes confer susceptibility to breast cancers. But unfortunately, the BRCA genes have not yet provided real breakthrough in our understanding of pathogenetic mechanism. Colorectal cancer looks somewhat brighter. Here the mismatch repair defect caused by mutations in several genes occur not only in the main Mendelian form of colorectal cancer (HNPCC) but also in a sizeable proportion (up to 20%) of sporadic cancer. These mismatch repair deficient colorectal cancer patients have a better prognosis than others (De la Chapelle 2001).

There are also many difficulties specific to anticancer drug discovery. An effective chemotherapeutic agent must selectively kill tumor cells. Curative, non-cytotoxic drugs are but a dream. Few years back, inhibiting angiogenesis by blocking the action of proteins such as vascular endothelelial growth factor was thought to hold great promise in cancer treatment. But clinical trial of these drugs has so far been disappointing (Abbott 2002). Most anticancer drugs have been discovered by serendipity, and the molecular alterations that provide selective tumor cell killing are unknown. Even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies. We do not still understand why cisplatin, a DNA cross-linking agent, is an effective chemotherapeutic

agent for most germline testicular tumor (Hartwell 1997). In the pre-genomic era the compounds used for cancer treatment were DNA synthesis inhibitors, microtubule binders or molecules directly reaching DNA. This blunderbuss approach could cure some leukemia and a proportion of solid tumors. In the post genomic era cancer treatment contemplated to be more effective and specific for tumor cells compared to the normal. High-throughput screening platforms based on microarray and DNA chips are poised to significantly impact drug discovery process. However, it is to be remembered that most deaths from cancer are due to metastases that are resistant to conventional therapies (Fidler and Ellis 2000). So the real challenge will be to design drugs that would be effective in long-term basis, target specific and easily available to all.

Summary

In summary, expression array technology in the post genomic era will refine the classification of cancer to levels that classical methods have been unable to reach. Molecular bioinformatics will help us understand why some patients respond to radiations and chemotherapy, where as others are resistant. However, genomic medicine may not offer a quick fix 'cure' for various types of cancers and will be inaccessible to many living in the developing world. On the other hand, alternative medicine may become a prominent part of oncology in countries that have limited resources to fight the disease. Evidence shows that large portions of tobacco related cancers are preventable. Education the masses could lead to increase opportunity for early detection and prevention of cancer. Screening programs could greatly assist detection of cervical and breast cancer at early stages. Self-examination is a cost-effective method for early detection of breast cancer (Albert and Schulz 2003). However, ignorance and poverty are major stumbling block for control of cancer in developing world. Overcoming poverty is an insurmountable hurdle in the short term, while tackling ignorance with the necessary education is possible. Cancer awareness and screening thus deserves continuing high priority in terms of both research and application in the developing countries. New ventures may be built on possible expansion of IARC's role in prevention and intervention research into a "Global Science Force" by following the examples of cervix cancer screening trials in India (Vainio 2002) and China (Li et al 2000). WHO's support with its regional offices would be beneficial, together with further national funding and support, and research collaboration and funding from more wealthy countries.

References

Abbott A (2002). On the offensive. *Nature*, **416**, 470.

Anderson S, Hastings G, MacFadyen L (2002). Strategic marketing in the UK tobacco industry. *Lancet Oncol*, **3**, 481-6.

Albert US and Schulz KD (2003). Clinical breast examination: what can be recommended for its use to detect breast cancer in countries with limited resources? *Breast J*, **9(Suppl 2)**, S90-3.

Anon (2001a). India's new smoking laws-progress or politics? *Lancet Oncol*, **2**, 123.

Anon (2001b). Quick success for cancer kinase treatment. *Nature Med*, **7**, 637.

Bonetta L (2001). Anticancer squirt. *Nature Med*, **7**, 891.

Cantu JM (2001). Virtual Genomic medicine in developing countries. Proc. 10th International Congress Human Genetics, Austria, 67.

Cavalli F (1999). The future of oncology: more of the same. *Lancet*, **354 (Suppl IV)**, 42.

Das BR, Nagpal JK (2002). Understanding the biology of oral cancer. *Med Sci Monit*, **8**, 258-67.

De la Chapelle A (2001). Has gene detection benefited the cancer patient? Proc. 10th International Congress Human Genetics, Austria , 63.

Fidler IJ and Ellis LE (2000). Chemotherapeutic drugs-more really is not better. *Nature Med*, **6**, 500-2.

Gangopadhyay S, Mallik S (2003). Role of general practitioners in cancer management. *J Indian Med Assoc*, **101**, 756, 758- 9.

Ghooi RB and Ghooi SR (2003). Freedom from pain-a mirage or a possibility? Experience in attempts to change laws and practices in India. *J Pain Palliat Care Pharmacother*, **17**, 1-9.

Gilmore AB and Collin J (2002). The world's first international tobacco control treaty. *BMJ*, **325**, 846-7.

Hartwell LH, Szankasi P, Roberts CJ, Murray AW, Friend SH (1997). Integrating genetic approaches into the discovery of anticancer drugs. *Science*, **278**, 1064-8.

Kumar S (2004). Much health care in rural India comes from unqualified practitioners. *BMJ*, **328**, 975

Lazcano-Ponce E, Alonso P, Ruiz-Moreno JA, Hernandez-Avila M (2003). Recommendations for cervical cancer screening programs in developing countries. The need for equity and technological development. *Salud Publica Mex*, **4**, S449-S62.

Li H, Jin S, Xu H, Thomas DB (2000). The decline in the mortality rates of cervical cancer and a plausible explanation in Shandong China. *Int J Epidemiol*, **29**, 398-404.

Macek C (1984). East meets west to balance immunological yin and yang. *JAMA*, **251**, 433-41.

Mervis J (1996). Ancient remedy performs new tricks. *Science*, **273**, 578.

Mittra I (1997). Fight against cancer in countries with limited resources. *Eur J Cancer*, **33**, 511.

Moore P (2001). Cancer and the human genome: no quick fix. *Lancet*, **357**, 533.

Navarro V (2004). The world situation and WHO. *Lancet*, **363**, 1321-3.

Pal SK and Mittal B (2004). Improving cancer care in India: prospects and challenges. *Asian PacificJ Cancer Prev*, **5**, 224-6.

Pal SK and Mittal B (2003). Importance of complementary and alternative therapies in palliative oncology in India. *J Altern Complement Med*, **9**, 811-2.

Pal SK (2002). Use of alternative cancer medicines in India. *Lancet Oncol*, **3**, 394-5.

Rajagopal MR and Venkateswaran C (2003). Palliative care in India: successes and limitations. *J Pain Palliat Care Pharmacother*, **17**, 121-8.

Ratin MJ and Relling MV (2001). Gazing into a crystal ball-cancer therapy in the post-genomic era. *Nature Med*, **7**, 283-5.

Sagar SM and Wong R (2003). Chinese medicine and supportive cancer care: a model for an evidence-based, integrative approach. *Evidence-Based Integrative Med*, **1**, 11-25.

Smyth JF (2001). Science and serendipity in cancer research. *Eur*

J Cancer, **37**, 8.

Stewart BM and Kleinues P (Eds.). World Cancer Report. 2003, IARC Press, Lyon.

Vicker AJ and Cassileth BR (2001). Unconventional therapies for cancer and cancer related symptoms. *Lancet Oncol*, **2**, 226-32.

Wang CT (1990). Treatment of operated late gastric carcinoma with prescription of strengthening the patient's resistance and dispelling the invading evil in combination with chemotherapy: follow-up study of 158 patients and experimental study in animals. *Chung His I Chieh Tsa Chin*, **10**, 712-6.

Wilson CM, Tobin S, Young RC (2004). The exploding worldwide cancer burden: the impact of cancer on women. *Int J Gynecol Cancer*, **14**, 1-11.

Vainio H (2002). Social Responsibility in Cancer Prevention Research: IARC as a "Global Science Force". *Asian Pac J Cancer Prev*, **3**, 267-72.

Yach D, Hawkes C, Gould CL, Hofman KJ (2004). The global burden of chronic diseases: overcoming impediments to prevention and control. *JAMA*, **291**, 2616-22.

Zoon KC (2004). Future directions in cancer research: Impact of the completion of the human genome. *Toxicol Pathol*, **32 (Suppl 1)**, 1-2.