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Science and Affordability of Cancer Drugs and Radiotherapy in the World - Win-Win Scenarios

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1. Introduction

In the real world, there is an important step before seeing the effects and the outcome of cancer treatment. This step is to see that treatment become accessible and affordable for cancer patients. The rapidly increasing of costs of novel cancer drugs and radiation therapy equipment doesn`t commensurate with the slowly improvement of outcome. Thus, each advance in treatment, the magnitude of the increase in the cost of treatment exceeded the magnitude of improvement of efficacy. (Schrag, 2004). Pharmaceutical companies are developing costly novel cancer drugs that are marketed in the USA, Western Europe, and Japan with fewer markets and opportunities in Low and Middle Income Countries (LMICs). By the year 2020, among the 20 million new cancer cases, 70% will be located in the countries that have collectively, just 5% of the global cancer control resources. (Ferlay et al, 2010, Porter et al., 1999 & Stewart & Kleihues, 2003). At present, it is roughly estimated that at least half of cancer patients in the world have no access to cancer therapy. This situation is particularly marked –with variability – in LMICs. The problem is particularly tragic for Radiotherapy in sub- Saharan Africa where only 5% of cancer patients have access to radiotherapy (Elzawawy, 2008, Porter et, 1999). However, there are also variable proportions of cancer patients in high income countries like the USA who have difficulties in obtaining expensive cancer drug treatment and radiotherapy. (Bach, 2007 & Malin, 2010). There is no indication that the costs of these drugs will diminish in the future in the USA (Meropol & Schulman, 2007).

In the next decade, with the expected increase of numbers of cancer patients particularly in LMICs and with the increasing costs of treatment with novel drugs and radiation therapy particularly in LMICs, then, this situation would be aggravated and it could present more difficulties for all stakeholders; cancer patients, oncologists, health policy makers and governments, manufactures of cancer drugs and radiotherapy equipment and economists. This could cause difficulties for the wheel of advances in treatment and science and in marketing of innovation. Hence, a pressing need emerges for scientific initiatives. One of the recent scientific initiatives, in which most of representatives of the key international organizations are sharing in its meetings and development, is The Win-Win Scientific initiative that was proposed first by ICEDOC's Experts in Cancer without borders on December 2007. (ICEDOC is The International Campaign for Establishment and Development of Oncology Centers. www.icedoc.org). Breast Cancer is the most frequent

malignancy among females with about 1.4 million cases annually in the world. Multiple treatment modalities and drugs are used in its management (Ferlay et al, 2010 & Stewart & Kleihues, 2003). The present chapter focuses on updating the exploration of examples of the published and ongoing scientific researches and approaches that could lead to resource sparing and cost effective radiotherapy, chemotherapy and hormonal treatment of breast cancer as a model that could be expanded to other cancers in the world. Despite of all difficult challenges and the expected increase of problems of affordability and marketing of increasingly expensive cancer treatment, we aim at developing win-win scientifically based initiative and scenarios in which the interests of the main stakeholders are really considered. We stress on the notions of not compromising the overall outcome of treatment and to pay attention to the ways of its assessment in different parts of the world. North-North, North-South and South-South scientific collaboration are warranted in order that more cancer patients in the world would have access to cost effective treatment tailored to realistic conditions of each community.

2. Resource sparing in radiotherapy for breast cancer

2.1 Postoperative – post mastectomy and post lumpectomy – radiotherapy of breast cancer

2.1.1 Altered fraction schedules

2.1.1.1 Shorten fractionation for postoperative radiotherapy (Hypofractionation)

An example is The UK standardization of breast radiotherapy (START) randomized trial B. Between 1999 and 2001, 2215 women with early breast cancer (pT1-3a pN0-1 M0) at 23 centers in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 20 Gy over 5 weeks or 40 Gy in 15 fractions of 267 Gy over 3 weeks. Women were eligible for the trial if they were aged over 18 years, did not have an immediate reconstruction, and were available for follow-up. Randomization method was computer generated and was not blinded. The protocol specified principal endpoints were local-regional tumor relapse, defined as reappearance of cancer at irradiated sites, late normal tissue effects, and quality of life. Analysis was by intention to treat. This study is registered as an International Standard Randomized Controlled Trial, number ISRCTN59368779. The study showed that the radiation schedule delivering 40 Gy in 15 fractions offer rates of local-regional relapse and adverse effects at least as favorable as the standard of 50 Gy in 25 fractions (The START Trialists' Group, 2008). However, it is critical to realize that the late effects produced by RT are strongly related to dose per fraction. Therefore, higher dose per fraction increases the susceptibility of normal tissues to RT. It is for this reason that the data on late lung and cardiac morbidity and survival rates is very important when hypofractionated regimens are employed in breast cancer. The Oxford meta-analysis has reported that RT reduced the annual mortality from breast cancer by 13% but increased the annual mortality rate from other causes by 21%. Also, this increase was due primarily to an excess number of deaths from cardiovascular causes (Early Breast Cancer Trialists' Collaborative Group, 2000). By radiobiological rationale, hypofractionation has the potential for worsening cardiovascular side effects. Furthermore, the cardiac side effects take up to 15 years to manifest completely after treatment and persist well beyond this period (Munshi A. 2007). The hypofractionation in post mastectomy or lumpectomy radiotherapy has not been applied in the vast majority of centers in the world. This strategy will however be watched with keen interest since it has the potential to drastically reduce treatment times and has

important financial implications. (Munshi, 2009). There is a midway solution that could be also reasonable particularly for LMICs; the fractionation of 45 Gy in 18 fractions –used in Port Said, Egypt- which is adopted from the fractionations practiced successfully along years since the seventieth in many French centers (Sarrazin et al., 1989)

2.1.1.2 Accelerated partial breast irradiation (APBI)

Although hailed as a paradigm shift, the breast conservative treatment that emerged in the 1980s was in fact an extension of the Halstedian concept, wherein whole-breast irradiation (WBI) compensated for the limited surgery. Observations that 80-90% of breast recurrences after breast conservative surgery and WBI occur in the tumor bed questions the need for protracted elective WBI, and provides the rationale for accelerated-partial-breast irradiation (APBI) of small cancers without adverse features predisposing to multicenteric recurrence. APBI would mark a paradigm shift and a major advance in treatment. This would allow many more women to opt for breast conservation, resolve the dilemmas regarding chemotherapy and radiotherapy sequencing and perhaps would be more cost effective. (Sarin, 2005). Several techniques including multicatheter interstitial brachytherapy, intracavitary brachytherapy, intraoperative radiation therapy, and 3D conformal external beam radiation therapy have been proposed, and each of them has its own advantages and drawbacks. Although APBI is increasingly used in the United States and Europe, and the short-term results are promising, its equivalence with whole breast radiation therapy is not fully established. In addition, because the average breast size in some countries like Japan is considerably smaller than in the West world, the application of APBI to Japanese patients is technically more challenging. At this point, APBI is still an investigational treatment in Japan, and the optimal method of radiation delivery as well as its long-term efficacy and safety should be clarified in clinical trials (Mitsumori & Hiraoka, 2008). Our point of view is that in LMICs, breast cancer cases are usually more advanced than in the West and the price of machines would be expensive. However, we suggest thinking about the manufacture of a low cost 50 KV Radiotherapy machines adapted for the use in some middle income countries and that could be used for some other indications too.

2.1.1.3 Concurrent boost radiotherapy (CBRT) during the course of whole-breast radiotherapy (WBRT)

It implies giving boost radiotherapy concurrently during the course of WBRT itself instead of giving it sequentially after WBRT. There are different ways to deliver CBRT. A study was done to shorten the relatively long duration of treatment by delivering a concomitant boost (CB) to the tumor bed on Saturdays (Jalali et al., 2007). Thirty patients with locally advanced breast cancers suitable for breast conservation following neoadjuvant doxorubicin / epirubicin chemotherapy (CAF/CEF) were accrued in the study. Conventional RT (CRT) to the whole breast was delivered 5 days a week to a dose of 50 Gy, using 6-10 MV photons. In addition, an electron boost to the tumor bed was delivered every Saturday (12.5 Gy/5 fractions, weekly fraction on Saturday). With this, the entire RT treatment was completed in 5 weeks instead of the usual 6 weeks. All patients completed RT within the stipulated time with no grade IV skin toxicity in either group. CB did not significantly affect the global cosmetic results as compared with the CRT group at the end of 3 years (P=0.23). In another study, 52 patients with early-stage node-negative breast cancer were enrolled. The RT dose to the whole breast was 40.5 Gy in 2.7 Gy/fraction with a CB of 4.5 Gy in 0.3 Gy/fraction. With this, the entire RT

treatment was completed in 3 weeks No acute Clinical toxicity criteria (CTC) grade III or IV and no late soft tissue toxicity were noted. The cosmetic results observed were good to excellent. (Chadha et al., 2007). These studies demonstrate that giving a CB during whole-breast RT is a viable resource-sparing option and does not lead to any detriment in local control and cosmetic outcome. (Munshi. 2009)

2.1.2 Less number of radiation fields

Since systemic adjuvant therapy is given to most patients today, the traditional radiotherapy technique has been modified, many authors no longer recommended that patients who have undergone complete or level I/II axillary dissections should receive full axillary radiotherapy since survival is not improved and the risk of lymhoedema is increased. Also, the isolated internal mammary chain failure is rare even when radiotherapy is not given (Truong et al., 2004). However, still areas of controvert exist regarding irradiation of the regional lymph nodes (Axillary, supraclavicular and internal mammary lymph nodes). The Applied Radiation Biology and Radiotherapy (ARBR) Section of the Division of Human Health, International Atomic Energy Agency (IAEA), pays great attention to resource sparing strategies in cancer radiotherapy. One of the on-going important multicentre randomized studies is about resource sparing in breast cancer treatment. It is started in the year 2007. This study is comparing irradiation of the chest-wall only versus irradiation of the chest-wall and the supraclavicular field in patients who underwent a mastectomy. In addition, the ARBR Section is conducting clinical trials in cervical cancer, oesophagus, lung, rectal, glioblastoma multiforme, nasopharyngeal cancer and painful bone metastasis.

2.2 Palliative radiotherapy of painful bone metastasis

2.2.1 Single versus multiple fractions

Radiotherapy remains the main modality of management for symptomatic bone metastases. The goal of radiotherapy in such cases is to provide pain relief and optimization of quality of life (QoL) with minimal displacement, discomfort, hospitalization, morbidity for patients and minimal cost and time commitment as well. Performance status and degree of systemic disease must be considered prior to treatment. (Janjan et al., 2009 & Fairchild & Stephen, 2011). Approximately 25 randomized clinical trials and three meta–analysis have demonstrated equivalency of single and multiple fraction radiotherapy for bone relief from uncomplicated bone metastases. Other advantages of single fraction include decreased cost and lower risk of acute effects (Chow et al., 2007). The single fraction is preferred when examining the cost utility, but there is higher rate of retreatment associated with single-fraction radiotherapy (Van den Hout et al, 2003). In a randomized clinical trial with two palliative radiotherapy regimens 8 Gy/I fraction versus 30 Gy/10 fractions, the overall responses were 75% and 86% successively while the rate of re-treatment were 28% and 2% successively. (Foro et al, 2008). Similar results were obtained from a prospective randomized multi centeric trial in which the total number of patients was 376. The rate of re-treatment (15%) was also higher in the group of Single 8 fraction than the rate of retreatment (4%) in the group treated with 30 Gy/10 Fractions. (Kaasa et al. 2006). However, most authors recommend multiple fractionations for primary treatment of complicated bone metastases for which there is no surgical option, or for postoperative treatment. The goals of postoperative radiation therapy are to decrease pain, promote healing and minimize the risk of progression (Fairchild & Stephen, 2011).

It is worthwhile to note that the treatment of asymptomatic bone metastases may deferred unless the patient is at risk of a serious adverse outcome such as spinal cord compression or impending pathological fracture (Janjan et al., 2009).

2.2.2 Half-body irradiation

Retrospective and prospective phase I and II studies suggest that single dose (6-8 Gy) hemibody irradiation provides pain relief in 70-80% of patients with multiple sites painful metastases. Studies also report decreased opioid use and need for localized external beam radiotherapy. Patients should be premedicated with intravenous fluid, antiemetics, corticosteroids and analgesics in case pain flare. Sequential treatment of both upper and lower Hemibody Irradiation requires a 6 weeks gap for recovery of myelosuppresion. (Fairchild & Stephen, 2011)

2.2.3 The follow up of radiotherapy of bone metastases

According to the International bone metastases consensus working party recommendation, the determination of response is clinical, thus biochemical or imaging studies -with subsequent costs- are not routinely required in follow up. (Chow et al., 2002).

2.3 General measures

These could be done by the local professionals and health authorities or in consultation with regional and/or international institutions and organizations particularly The International Atomic Energy Agency (IAEA) and its Applied Radiation Biology and Radiotherapy Section (ARBR) and The Program of Action for Cancer Therapy (PACT). These include:

2.3.1 General strategic planning of radiotherapy facilities in developing countries

In a Consultation to the World Health Organization, a global strategy for Radiotherapy was proposed. It considered different local parameters including the Gross National Product GNP per Capita that categorized countries in the world into 4 groups (Levels). Accordingly series of three tier radiotherapy service was proposed, with internet-based intercommunication strategy (Porter et al., 1999). One of the interesting proposal that goes with the three tier system is the creation of an integrated three-tier radiotherapy service, which consists of primary, secondary, and tertiary radiotherapy centres in developing countries—coordinated through a teleradiotherapy network. Such a network could be cost effective, help to bridge the gap, and give all patients access to the state-of-the-art technology in radiotherapy (Datta & Rajasekar, 2004). The Breast Health Global Initiative (BHGI), suggested four levels for availability breast cancer management; Basic, Limited, Enhanced and Maximal (Anderson et al., 2006, Anderson & Cazap, 2009 & Bese et al., 2008).

2.3.2 Practical modifications of the system of work in radiotherapy departments

These are in order treat more numbers of patients, like to increase the hour work of cobalt machines in developing countries, the increase the number of fractions a week from 5 to be 6 fractions in certain applications (Overgaard et al., 2006), the reduction of Machine down-time in many developing country institutions that is mainly due to problems of maintenance and lack of culture of local regular preventive maintenance (Bhadrasain, 2005). In our view, we emphasizes on **the** importance of programs that should developed in order to assure that most of the problems of down-time of machines would be fixed in the soonest as

possible by the local teams either solely or and with prompt telecommunication with manufcturer maintenance staff.

2.3.3 Professional training

Customized and regular updating training are recommended for the local medical and technical staff and maintainers (Bhadrasain, 2005 &Porter et al., 1999). This because the local staff -and not the sophistication in machines- are the back bone of resource sparing and successful cost effective treatment for more number of patients.

2.4 Future directions regarding radiotherapy

From the above cited points and examples, and by rough estimation, and without additional high resources, the number of breast cancer patients treated by the present existing facilities of radiotherapy could be nearly doubled particularly in middle income countries. This could increase the cost-effectiveness of radiotherapy in the world and hopefully would be a stimulus for increasing facilities of radiotherapy in the world.

It is estimated that at least 5,000 additional radiotherapy machines are presently needed worldwide and, by 2015, at least 10,000 radiotherapy machines may be needed to meet growing treatment demand. It is estimated that during the upcoming 20-year,it is estimated that 100 million cancer victims in the developing countries will require radiotherapy, for cure or the relief of symptoms such as pain and bleeding. Sadly, only 20-25% of patients in developing countries that need radiotherapy can access it today, and the situation will only worsen in the future unless steps are taken to address it (Bhadrasain, 2005 & Yip, 2011).

In a recent study done in the US, only 77.6% of breast cancer patients received RT among the 135 patients undergoing mastectomy with strong indications. One of the causes of not receiving radiotherapy is the socio-economic condition (Jagsi et al.,2010). Hence, even in the US there are disparities in access to radiotherapy, but, surely it is not comparable with the situation in LMICs. In well-developed countries today, around one-half of the cancer patients require radiotherapy. In developing countries, however, an even greater proportion require radiotherapy due to the location and relatively advanced stages at presentation of many common cancers, which precludes adequate treatment by surgery alone (Bhadrasain, 2005 & Porter et al. 1999). Contrary to belief, radiotherapy is a cost-effective and not that expensive, it is salient to note that the cost of one military jet would represents the entire costs of radiotherapy for a country in some of parts of the world (Porter et. al. 1999).

Developing countries should evolve their own evidence-based guidelines and cost sparing in cancer treatment. For example, chemo-radiation of solid tumors in the nutritionally deprived patient may not accrue the same level of benefit as seen in the literature from affluent countries Clinical trials conducted in developing countries can most appropriately address these important questions in a scientifically robust manner. Ideas for such studies are always welcomed, even from individuals. Clinical investigators from developing countries are the key to appropriately addressing those challenges, by the rational utilization of radiotherapy and allied technologies - both new and old (Bhadrasain, 2005). Furthermore, The PACT/IAEA has formed recently an Advisory Group for Increasing Access to Radiation Therapy in Developing Countries (AGaRT), that includes international experts from organizations, national representatives and in collaboration with manufactures. ICEDOC is represented in this promising effort of PACT that -hopefully- if the international will, science and the interests of stakeholders including the manufacturers

come together in a win-win environment to achieve feasible objectives, then, it could be a turning point in the history of affordability of Radiotherapy of cancer in many underserved regions in the world.

3. Cost sparing in Breast Cancer Systemic Therapy (BCST)

In reviewing the current literature, we provide examples of innovative ideas, evidence-based approaches, and ongoing efforts that could decrease costs of BCST without compromising outcomes.

3.1 Relatively recent and expensive drugs

3.1.1 Evidence based cost effective indications of drugs

An example is the limitation of the use of Trastuzumab in breast cancer to women with non-metastatic disease and known HER2/neu positive status (Yarney et al., 2008). Limiting the use of Trastuzumab to women with ERBB2 positive status is cost effective measure, even with the additional associated cost of the test (de Sousa & Bines, 2009). Nevertheless, in the United States, a recent study revealed that up to 20% of patients receiving Trastuzumab were never tested nor had any documentation of a positive test result (Phillips et al, 2009).

3.1.2 Shorter course of treatment

An example is the shorter course of trastuzumab. The optimal duration of adjuvant trastuzumab therapy remains undetermined. There are trials in progress comparing 52 weeks of trastuzumab with 9 weeks, 3 months and 6 months. The FinHer (Finland Herceptin) study indicated that a 9-week period of trastuzumab administration is effective in women with HER2/neu-positive breast cancer. This means saving of around 80-90% of the cost of longer course (Joensuu et al., 2009). This is in addition to less total time of hospitalization, less risks of cardiac toxicities due to trastuzumab and less cost of the subsequent supportive treatment due to longer courses.

3.1.3 Pharmacokinetic studies to lower the dose by changing regimen of infusion

This is based on application of the pharmacological information and how the drug is transformed to its active ingredient in the body. An example is the low dose, prolonged infusion of gemcitabine. Hence, the habitual dose of 1000-1250 mg/m^2 for one patient could be enough for 4-5 patients. Phase I–II trials of low dose gemcitabine in prolonged infusion (of 250 mg and 180 mg/m2 for 6 and 24 h, respectively) and its comparable results in responding solid cancers like non-small cell lung cancer, breast, pancreas, and bladder cancers are encouraging. The explanation lies in the saturation of the enzyme deoxcytidine kinase needed for conversion of gemcitabine into its active form gemcitabine triphosphate, which occurs after short conventional infusion and leaves most of the drug unmetabolized (Zwitter et. al, 2005 & Khaled et al, 2008).

3.1.4 Dugs interactions and pharmacokinetic based studies

Lapatinib is an oral dual tyrosine kinase inhibitor of both epidermal growth factor receptor and *ERBB2*, approved for advanced *ERBB2*-positive breast cancer after failure of trastuzumab treatment. Pharmacokinetic-based studies include the example that showed

that lapatinib taken orally with food and beverage containing CYP3A such as grapefruit juice, and not on an empty stomach as stated on the label, results in increased plasma levels and could reduce the dose and costs of lapatinib by 80%. Hence, for this expensive drug the habitual dose for one patient which is around 1250-1500 mg per day, could be enough for five patients, in addition to save cost of treatment of diarrhea due to lapatinib. It was suggested that the diarrhea is caused by the unabsorbed drug in the gut (Ratain and Cohen, 2007). Pharmacokinetic studies that pursue ways to enhance bioavailability of agents could markedly decrease the required doses and subsequent cost of treatment. Strategies include the support of clinical trial processes to pursue evidence to support less costly and optimal therapeutic efficacy outcomes (Elzawawy, 2008 & 2009).

3.1.5 Interrupted courses

Potential research questions include the interrupted courses of Aromatase inhibitors (AI) that probably would be also effective as continuous therapy after prior Tamoxifen and/or AI treatment. The hypothesis is that AI interrupted courses perhaps could enhance response of residual resistant cells (Colleoni and Maibach, 2007). This area is still in need for more researches. It could be the occasion to cite another example in another cancer i.e. prostate cancer, with different hypothesis. In a phase III randomized trial comparing intermittent androgen suppression IAS versus continuous androgen suppression for patients with PSA progression after radical radiotherapy. IAS was delivered for 8 months in each cycle with restart when PSA reached >10 ng/ml off treatment. Overall survival (OS) was not inferior in the arm of IAS, with improvement of quality of life (QoL), reduced hot flahes. Time to hormone refractory state (HR) was statistically significantly improved on the IAS arm (Klotz et al., 2011).

3.2 Essential drug, relatively cheaper and conventional systemic cancer drugs

Fortunately, the pharmaceutical arsenal of "essential and conventional systemic anticancer drugs" still constitutes the basis of systemic treatment of cancer. In addition, these conventional drugs are relatively inexpensive. For breast cancer the list would include CMF (Cyclophosphamide, Methotrexate and 5 Fluorouracil), FAC (5 Fluorouracil, Doxorubicin and Cyclophosphamide), Tamoxifen and Ovarian ablation. Innovative strategic thinking and approaches should be encouraged to improve the availability and accessibility of first-line systemic anticancer treatments as part of the comprehensive breast cancer control plan for underserved regions (Elzawawy, 2009).

3.2.1 Is anthracycline-based chemotherapy standard as adjuvant breast cancer treatment?

Six cycles of anthracycline-based chemotherapy was considered a standard in adjuvant treatment of breast cancer. However, there is data to suggest that not all patients will benefit from anthracyclines. In a recent study, patients who were Her2 negative did not gain any added benefit from addition of anthracylines as compared to regimens employing CMF (Cyclophosphamide, Methotrexate, and 5 Flourouracil) (Paik, 2008).

3.2.2 Chemotherapy versus ovarian ablation as adjuvant breast cancer treatment

Randomized studies over the past decade have demonstrated that ovarian ablation/suppression equivalence is at least equivalent to CMF regimens in receptor-

positive premenopausal patients (Munshi, 2009). In a recent randomized study that included patients with large tumor sizes and nodal positivity, nine cycles of CMF were equivalent to RT-induced ovarian ablation. The study included 762 women who were premenopausal, were hormonal receptor positive, and were at high risk of relapse (defined as metastasis to at least one lymph node or tumor > 5 cm). The patients were randomized to receive either ovarian ablation by RT or chemotherapy with nine cycles of intravenous CMF. A total of 358 first events were observed: 182 in the ovarian ablation group and 176 in the CMF group. The unadjusted hazard ratio for disease-free survival in the ovarian ablation group compared with the CMF group was 0.99 (95% CI: 0.81 to 1.22; $P = 0.95$ by the log rank test). Median disease-free survival time was 130 months in the ovarian ablation group compared with 122 months in the CMF group. After a median follow-up of 10.5 years, the overall survival was similar in the two groups, with a hazard ratio of 1.11 (95% CI: 0.88 to 1.42) for the ovarian ablation group compared with the CMF group. No significant correlation was demonstrated between treatment modality and hormone receptor content, age, or any of the well-known prognostic factors. This strategy may be considered in a low-risk, young, premenopausal woman, whose compliance for chemotherapy is doubtful, and who has a strongly hormone-sensitive tumor. The readily apparent gains from this approach are that repeated visits for chemotherapy can be avoided, as also the toxicity of chemotherapy; there is also considerable savings in cost for the patient or the Medicare. (Ejlertsen, 2006). The ovarian ablation by radiotherapy could be done by simple technique, in 4-5 fractions, during or after the course of post mastectomy or lumpectomy radiotherapy to breast/chest wall. Also, it could be done by surgical ablation.

3.3 The oral route for administration of chemotherapy

The oral forms of chemotherapy could lower the cost of patient transportation, administration, hospitalizations, the subsequent costs of adverse effects of hospitalizations and it may improve the quality of life (Elzawawy, 2008 and Elzawawy, 2009). In fact, this point could be applied to old and new cancer drugs. More pharmacological and clinical researches as well as in manufacture of drugs are warranted. Hence, most known cancers could have regimes of treatment that are totally or partially administrated via oral route. The pros and cons of oral route administration of chemotherapy should be carefully studied in each community in a scientific and realistic ways. Questions of cost-effectiveness and best practices relating to oral and self-administered agents are of considerable interest in LMICs where facilities and providers may be particularly scarce. One of the major realistic obstacles is not the compliance, which should not be taken as an absolute and undefeatable problem in some population, but also, the factors related to oncologists and hospitals with less gain from oral therapy. In a win-win initiative all factors and interests of all stakeholders should be tackled in realistic, transparent, scientific and global ways.

3.4 Genomics and cancer treatment

Pharmacogenomics is the study of individual genetic variation in efficacy and adverse effects of a drug. Radiogenomics is reffered to the same science but for radiotherapy. This science offers a partial explanation for the interpatient variability in treatment response commonly observed in oncology. Small variations in patient germline DNA sequence (genotype), including single nucleotide polymorphisms (SNPs), can alter the expression and functional activity of an encoded protein. Often, genetic variants leading to clinically

relevant functional changes occur in noncoding (intron) regions of the genome or in exons that code for protein expression (Guttmacher& Collins, 2003). These changes may lead to individual differences in drug distribution, metabolism, activity and toxicity (Connolly& Stearns, 2009, Lash et. al, 2009).

Pharmcogenomic studies were suggested to guide the adjustment the effective use of some drugs like Tamoxifen (Colleoni, 2002 & Lash, et al, 2009). Patients can be classified as poor, intermediate, or extensive metabolizers according to the genetic variation in CYP2D6, a key enzyme in Tamoxifen metabolism. In the poor metabloizers cases, the use of Tamoxifen, would be a waste of costs for 5 years of probably non sense treatment and with unnecessary risks of hazards. In the other hand, a modeling analysis suggested that the benefit of 5 years of adjuvant Tamoxifen therapy in patients who were carriers of the wild-type CYP2D6,the extensive metabolizers, was similar or perhaps superior when compared with the more expensive aromatase inhibitor therapy. Thus, it was suggested that onetime test for CYP2D6 genotype has the potential to make the patient eligible for 5 years of savings by allowing for the use of -the less expensive- Tamoxifen (Punglia et al., 2007). However, more prospective studies about CYP2D6 and this topic are warranted, as recently there are controversies regarding the significance and value of the adoption of routine CYP2D6 testing in the clinic (Lash et al., 2009). Science is searching for the truth. The road for facts is endless and enjoyable. In fact, once again, not every exciting scientific finding could be translated into the same expected clinical value in the short and the long term clinical researches and trials (Elzawawy, 2010 & 2011).

Besides probable different variations in human host and tumor biology, real local socioeconomic conditions and priorities of problem, cost effectiveness, cost utilty, available services including supportive treatment different, Pharmcogenomics and Radiogenomics are among the possible causes of that protocols and guidelines of treatment shouldn't be copied in different communities without adaptation and without considering these factors in scientific and realistic ways.

3.5 Generic equivalents for off-patent drugs

The World Health Organization (WHO) proposed essential drugs required for cancer therapy (WHO, March 2010). Many drugs included in the 'Essential Drugs for Cancer Therapy' list have generic equivalents that offer the possibility of less expensive treatment. However, we stress on not taking the proposal of using generics off patent cancer drugs as a magic stick and automatically as an ideal solution for more cost effective treatment, without assuring the flow of production and the affordability of generics drugs of good quality. Particularly in developing countries, the quality and bioequivalence of generics drugs should be assured by regulations or developing a transparent system for international testing. A generic of good quality or an "original" essential drug would be more cost effective than generics of less quality, even if the later is of fewer prices. Also, the use of first line treatment of tested good quality drugs could reduce the needs for second and third lines treatment that are usually more expensive. Besides, the risk on patients, results of clinical trials and researches in LMICs would be doubtful if they are done with drugs with questionable quality. We suggested an international body or experts or programs that would assure the quality and bioequivalence of generics delivered to LMCIs. To overcome difficulties in achieving large scale feasibility in quality control, we suggested small scale groups level to test random samples or pilot settings upon invitation from the local

authorities in some developing countries. Hence, it wouldn't be to police, but to advise and it would react only upon request from the locals (Elzawawy, 2008 & 2009).
Contrary to belief, the availability of essential and generics off-patent cancer drugs is very critical issue to rich and developed countries and not only for developing countries. In November, 2010, the American Society of Clinical Oncology (ASCO) announced that across the United States, there is severe and worsening shortage of a big group of these drugs that are placing cancer patients in the US at risk, including –and not limited to- doxorubicin, carboplatin, cisplatin, etoposide, leucovorin, nitrogen mustard, vincristine and morphine. Michael Link, MD, president-elect of ASCO, for the term 2011-2012, said in a statement "Shortages of critical cancer drugs are causing delays in treatment, which can impact survival and the ongoing clinical trials. Additionally, administration of alternative therapies, if they are available, can lead to less optimal treatment, as well as increased costs, for patients and increased administrative burdens for oncology practices". Bona Benjamin, from the American Society of Health System Pharmacists (ASHP) stated "For hospital pharmacists, the shortage of injectable cancer drugs products — many of which have no therapeutic alternatives — is approaching a national crisis in the US. There is no single reason or solution for the shortages. Most of the cancer drugs that are in short supply are generic products and are manufactured by a few companies. There is no financial incentive to manufacture cheaper generic drugs. In a free market, there is nothing to compel manufacturers to make drugs that don't make them money; there is no hammer". (Chustecka, 2010). One of the values of having global scientific approaches for the problems of availability and affordability of cancer is that we could explore and tackle proposals that could help –with variations- in developing and developed countries. The Win-Win initiative concentrates on scientific approaches that could lead finally to the benefit of all stakeholders.

3.6 Old cancer drugs, new uses, news profits

By scientific approaches, old cancer drugs could have new indications, and subsequently offering less expensive treatment to cancer. This implies exploring new indications or innovative combinations or different schedules of administration of older (and relatively cheaper) previously approved cancer. For example, the relatively old like cisplatin has been shown to be useful in the treatment of triple negative (-ve estrogen and progesterone receptors, HER2/neu 0, 1) breast cancer (Gronwald et al., 2009). The metronomic use of prolonged, low oral doses of the cheap drugs cyclophosphamide and methotrexate are used as palliative breast cancer treatment (Colleoni, 2002). In a recent phase II trial, the low dose (6 mg/d) oral estradiol was effective (around 30%) as conventional high dose (30 mg/d) with less adverse events in postmenopausal women with advanced, aromatase inhibitor-resistant, hormone receptor-positive breast cancer (Ellis, 2009).

3.7 Old non cancer drug, new uses in cancer, potential new profits

An example is inexpensive drug called metformin. It's widely used by type 2 diabetics who overproduce insulin. But new researches suggest that it could be useful in breast cancer prevention and treatment. It was found that metformin can also act on lung cancer tumour growth in mice that have been exposed to a common carcinogen in cigarettes. Moreover, new studies suggest that it could be tested for colon cancer too. It's thought the drug works by targeting a cancer tumor's stem cells which, if not killed off, can allow various cancer cell

types to regenerate. Hence, have an old molecule, an old drug, a safe drug that may have an unexpected use in cancer prevention and cancer treatment. More studies are currently planned. Each tablet costs 21 cents and must be taken twice daily. Despite the low price, the cost to run such a clinical trial, which involves collecting blood samples, is expected to run at least $15-million. The trial is expected to include 3,582 patients in Canada and the United States who are undergoing standard cancer treatment plus metformin or placebo for up to five years. Until the results are in, patients should not use it unless it is prescribed for diabetes or they are on the clinical trial, where they can be properly monitored (Dowling, 2011).

3.8 New uses for cancer chemotherapy drugs in non malignant indications

An example is the recent researches that revealed that fluorouracil could be used as a skin cream to help repair of sun damage and skin wrinkles on the faces. Topical fluorouracil causes epidermal injury, which stimulates wound healing and dermal remodeling resulting in improved appearance. The mechanism of topical fluorouracil in photoaged skin follows a predictable wound healing pattern of events reminiscent of that seen with laser treatment of photoaging (Sachs et al., 2009)

4. Does evidence-based medicine really reduce costs?

The question is paused by many from time to time. In a wonderful recent article the issue is discussed (Kolodzie, 2011). Till recently the issue was a theory and a hypothesis. It pass now to the phase of having proof. The adoption of pathways based on evidence-based medicine (EBM) in patients with non–small-cell lung cancer (NSCLC) revealed that evidence-based care resulted in an average cost-savings of 35% over 12 months and equivalent outcomes (Neubauer et al., 2010). It is important to note that not all pathways are created equal. Most programs use minimum criteria to develop their pathways; these typically include assessment of efficacy and toxicity. A few pathway programs go beyond these minimum criteria and consider costs as well. These types of programs delineate treatment options based on maximum survival benefits, minimal toxicity, and cost-saving advantages.

4.1 Reduction in expensive supportive care drugs

When two or more therapies are equally effective against a disease, regimens lower in toxicity are typically chosen to be on-pathway. This leads those physicians who adhere to pathways to be less likely to prescribe expensive anti-emetics, growth factors, and other supportive care drugs absent strong evidence to validate their use.

4.2 Fewer hospital visits

One of the most common reasons patients require hospitalization during treatment is adverse effects and complications caused by the agents. The less toxic on-pathway regimens can result in fewer or less severe adverse reactions, therefore reducing the number of unplanned hospital visits.

4.3 Reduction in therapy overall

Treatment guidelines, backed by evidentiary support, lead physicians to confidently recommend the most effective therapy as the first-line treatment with standard order sets

that define dosing strengths and number of cycles. For many cancers, especially solid tumors in adults, each successive line of treatment is less efficacious than the preceding line. When patients with late-stage disease face difficult decisions, some will wish to continue a line of treatment no matter what. Others express the desire to improve their quality of life, with many stating that they prefer to die at home rather than in the hospital. (Wennberg et al., 2008). Third and fourth lines of treatments rarely change the course of the disease and can cause incapacitating adverse effects. More often than not, if a patient's cancer has not responded to or has progressed after the first or second line of treatment, the best course for that patient may be to transition into end-of-life or palliative care. A study analyzing Medstat 2007 data in the US, revealed that out of those chemotherapy patients with 10 major cancer diagnoses who were identified as dying in an inpatient setting, 24% received chemotherapy within 14 days of death and 51% received chemotherapy within 30 days of death (Fitch & Pyenson, 2010). While we cannot always predict when death will occur, pathways can help guide physicians in making decisions and treatment recommendations pertaining to whether to offer additional cycles of a treatment or move to second, third, and further lines of treatment. They can also provide practical guidance that can be helpful in end-of-life care discussions. This includes demonstrating that transitioning to hospice care can improve the patient's and the family's quality of life and can reduce the costs borne by the family and payers by avoiding unnecessary and ineffective chemotherapy administered within a few weeks of death (Kolodzie, 2011).

4.4 Use of less expensive drugs

Oncology drug costs are exorbitant, making this line item an obvious target for payers as they search for ways to reduce costs. One way in which EBM can help reduce the costs of cancer care is by optimizing the appropriate use of less expensive drugs. When pathways are developed, it will often be found that evidence supports the use of less expensive therapies, without compromising outcomes or increasing toxicity. For example, if treatment pathways point to two potential therapies that are largely equivalent in efficacy and toxicity, yet these two drugs vary enormously in cost, pathways programs that consider cost a factor would ultimately point to the less expensive drug. Obviously, there are some cases in which cost cannot be a determining factor in deciding which drug to use to treat a patient. Where one therapy is far more effective than others, it is the clear choice and will be indicated as the first choice for that setting. Take trastuzumab as an example. Trastuzumab is unquestionably an expensive drug, but evidence for its efficacy in certain situations is indisputable. As pathways are developed, efficacy is given the highest priority, with cost being considered only when outcomes are equivalent. In the case of trastuzumab, the efficacy of the drug and the lack of available substitutes make it the correct choice- when it is used in appropriate indications- regardless of its price.

5. Control of utilization of a drug as a primary strategy of Medicare, USA

The primary strategy Medicare uses to hold down utilization of a drug (or another health care good or service) is to limit coverage of payment for it. The program does so by actively determining in which settings the drug is or is not "reasonable and necessary" through either a single national or one or more local coverage decisions. When these coverage decisions result in restricted guidelines for the use of the drug, the result is decreased utilization. For instance, in 2007, Medicare narrowed the coverage of erythropoiesis-stimulating agents

(ESAs) for cancer treatment. Medicare limited not only the types of patients who could receive ESAs but also the clinical scenarios in which they could be used (Centers for Medicare & Medicaid Services, 2007). One of the biggest companies who sale ESAs in the USA, reported to their investors in August 2007 that changes in coverage for ESAs by the Centers for Medicare and Medicaid Services (CMS) would reduce annual sales of the company's ESA from approximately $1 billion to $200 million among Medicare patients. In our view, the lesson here, is that if the strategy of control utilization is indicated in a rich country like the USA, then, it would be mandatory in less affluent countries. In a win-win scenarios, our objective is not at all against the sales of drugs per se, but this strategy of controlling utilization of drugs, by whatever the mechanism in each country, would assure more reasonable and justified utilization of drugs (or services). Otherwise, the chaos in its utilizations in some less affluent countries, opens wide doors for the use of these drugs when it is not necessary while omitting patients who are in real big need for these drugs, for more local corruptions and exhausting resources in non cost effective ways without marked improvement of outcome and in non cost effective ways, and finally it could lead to collapse of markets in those of countries in front of new products of companies. Hence, transparent scientifically based measures are encouraged by the win-win initiative for the benefit of all stakeholders.

6. Economic analyses and outcomes assessment

Economic analyses are most valuable to health policy analysis and health care managers who must allocate resources and established health care management. An economic health care analysis tries to directly relate the incremental cost of an intervention to its potential benefit. (Hayman et al., 1996). Clinical Oncologists shouldn't be away from knowing basic information and various terms of such issues. That is why –at least the definitions- are included in many cancer treatment textbooks or in chapters dealing with availability, accessibility and affordability of cancer treatment. Not surprisingly, high costs can be financially devastating to American patients and their families, with some 62% of all bankruptcies estimated to result from medical expenses (Himmelstein et al, 2009). The American Society of Clinical Oncology (ASCO) has issued a Guidance Statement affirming "the critical role of oncologists in addressing cost of care" and stating that "ASCO believes that communication with patients about the cost of care is a key component of high-quality care (Meropol et al.,2009). However, many oncologists feel ill-prepared to discuss the costs of therapy with patients, (Schrag &Hange, 2007) and little is known about how patients factor cost into their decision-making when facing a life-threatening crisis of a cancer diagnosis (Mileshkin, 2009).

6.1 Definitions of various terms used in economic analysis

6.1.1 Cost minimization

It relates to lower cost of an alternative treatment without regard to the efficacy. It is measured in dollars. The major drawback of only using this approach to evaluate cancer treatment is the fact that complex-oncology therapies almost never result in truly identical outcomes.

6.1.2 Cost benefit

It relates to the additional cost of treatment in dollars to its incremental benefit in dollars, as compared to the most reasonable alternative treatment. Results of cost benefit analyses also

can be reported as a ratio, where the additional cost of treatment is divided by its added benefit, again compared to the most reasonable alternative.

6.1.3 Cost effectiveness

It relates the additional costs of an intervention to its incremental impact on any clinically relevant measure of benefit. Because one of the primary uses of economic analysis is the allocation of limited resources among different choices, benefit often is measured in units that are universally applicable to all intervention. Years of life saved are the most commonly used measure. For example, the cost-effectiveness of combination chemotherapy, compared with single-agent therapy, for a given disease could be assessed by calculating the additional costs (in dollars or the monetary units) per additional patient reaching the 5-year disease-free survival mark or more frequently, per years of life saved.
The Incremental cost-effectiveness ratio (ICER) or The intervention's cost-effectiveness ratio is calculated by dividing its incremental cost by its incremental impact on survival, as compared to the most reasonable alternative treatment. The intervention's cost-effectiveness ratio, expressed in units of dollars per unit of effect compared to the standard intervention. Years of life saved are the most frequently used measure. Cost-Effectiveness ratios are, therefore, usually expressed in terms of dollars per year of life saved.

6.1.4 The QALY and the DALY

Medical interventions affect not only length of life but also quality of life (QoL). Cancer cure may be brought at the expense of substantial treatment-related morbidity. Conversely, palliative therapy may bring marked relief of symptoms; even it does not lengthen life dramatically. A nonmonetary unit for evaluation is the quality – adjusted life year (QALY). QALY measure the "usefulness "or "utility" of a health state and the length of life lived under those conditions. One attempts to obtain values or utility measures by expert opinion, by using values derived in previous studies, and by surveys of patients. These surveys can be difficult to construct and may involve asking patients to make a "time tradeoff" or engage in a "rating scale "of various conditions or to assign a preference weight on a scale of 0 to 1 to a condition. The DALY is the disability-adjusted life year. WHO has suggested that a health intervention can be considered cost effective if it yields savings of one disability-adjusted life year for less than three-times a country's gross domestic product (GDP) (Torres Edejer et al., 2003).

6.1.5 Cost utility

It relates the additional cost of treatment to its impact on both survival and quality of life, as well as productivity of the patient following treatment. The length of time spent in each outcome is multiplied by the outcome's weighting factor and the product is summed. A cost-utility analysis may be considered as special form of a cost-effective analysis. In the cost-utility analysis, the health outcome of the denominator is valued in term of utility or quality of life. The monetary units of evaluation include the QALY. It is common to express cost-utility analysis as total net cost per unit of utility or measure of quality – for example, a number of dollars or saving per QALY gained. A cost-utility ratio can be calculated by dividing its additional cost by its incremental change in QALYs, compared to a reasonable alternative. Hence, the units of the cost-utility ratio is Dollars/QALY.
We can conclude that over the past decade it has become increasingly clear that, in addition to quantity of life, the impact of treatment on quality of life must be incorporated into measures of benefit. (Hayman et al., 1996 & Weeks, 2003).

It worthwhile to note that the "no treatment" strategy does not necessarily mean it is a "no cost "strategy. Hence, in our view, contrary to belief, the affordability of well-tailored scientifically based treatment or appropriate palliation could -in many cases- reduce variable costs and burden of "no treatment". We hope that this message finds its way to local leaders of health policies decisions makers, leaders of global health departments in the world and in the United Nations Non Communicable Diseases (NCDs) meetings.

7. Health technology assessment (HTA) programs

HTA programs evaluate the value of new therapies and technologies to patients by considering the following (Hutton et al, 2006): Is the new treatment effective? Although surrogate end points such as response rate may be sufficient evidence of efficacy for regulatory agencies (eg, rise in hemoglobin after administration of erythropoietin stimulating agent), HTAs generally demand more direct evidence of benefit (eg, improved quality of life measured by a validated instrument, or improved survival). Which patients benefit? If the clinical trial population excluded particular patient populations, are they likely to have the same benefit as the patients included in the study? How does it compare to other available treatments? At what cost?

Many countries now incorporate HTAs into their decision-making process before deciding to cover new therapies within their publicly funded health care systems. The United Kingdom was the first country to adopt HTA explicitly by creating the National Institute for Clinical Effectiveness in 1999. Since then, many other countries, including Australia, Belgium, Canada, Denmark, Finland, German, Hungary, the Netherlands, Norway, Portugal, and Sweden, have developed processes for HTA to be used in coverage decisions. Although to date the information does not appear to have had much impact on formulary decisions, US private health plans are increasingly requesting pharmaceutical manufacturers to submit evidence dossiers that adhere to the Academy of Managed Care Pharmacy guidelines and include information on clinical and cost effectiveness (Sullivan et al., 2009)

8. Finally, we emphasize on these points

To enhance researches and scientific studies that result in decreasing the total cost of treatment and to increase –or at least not to compromise- effectiveness and quality of life. It is preferred to design -as most as possible- protocols of treatment that require less or no hospitalizations- except in some cases, less costs of auxiliary cares and expensive supportive drugs that could be not available in the community or it could produce high additional financial burden.

To develop more scientific researches that go with the notion of "Resource-level-appropriate use of costly agents" and that necessarily involves inclusion of how to mobilize the locally-available resources and the establishment of viable partnerships with different sectors in the community. Hence, LMICs shouldn't count on financial donations from far, as they would be never enough. The real lasting help to these communities is in assisting of local capacity building, for cooperative scientific researches, training, assistance in reporting and publications and appropriate technology transfer.

To test innovative combinations or different schedules of administration of older (and relatively cheaper) drugs that might lead to improve therapeutic index or newer applications in different societies. Such investigations usually are not supported by pharmaceuticals companies and international conferences, although they might be of benefit

to science and cancer patients in LMICs and affluent countries. Conducting such researches in LMICs would be a sort of capacity building for researches and clinical trials that could be used for conducting trials with appropriate ethical guidelines - and subsequent access - for newer drugs in these communities and it could pave the ways for justified use and sales of newer drugs in more cost effective ways in markets that risk to shrink in the upcoming years. Such approach would assist companies in streamlining the development of new drugs and technologies.

To disseminate the concept of global and balanced cancer control including earlier diagnosis and supportive and palliative care. Earlier diagnosis of less advanced cases could decrease the total costs of treatment and increase quality of life. But, screening and efforts for early detection without having affordable treatments that respect what we call "The economic and social dignity of patients and their families" would be fruitless and it would be frustrating for both patients and health professionals. (Elzawawy et al., 2008). Incidence of a particular cancer, total per-capita health spending (WHO, 2010), country's gross domestic product (GDP) should be considered in estimation cost-effectiveness of some screening programs like mammographic screening for breast cancer. Resources in LMCs might be better used to raise awareness and encourage more women with palpable breast lumps to seek and receive treatment in a timely manner and to assure patient navigator services in LMCs, which aim to help women access their health-care system and receive better care once in the system, could be more cost effective than attempts to screen the asymptomatic masses (Harford, 2011). Palliative care is an essential component of comprehensive cancer care (Becker et al., 2011). The availability of supportive and palliative care integrated oncology could improve outcome, reduce overall costs, lessen burden on patients and families and improve qualities of life and death.

Thinking is never enough. We have two preliminary proposals and we cite them here as questions for wider discussion. We suggest the term: "The Relevant Clinical Oncology". It considers the variability in biologic and pharmacologic factors among the human hosts and the nature of tumors, cost effectiveness and cost utility as well as the real socioeconomic conditions. It respects the expectations and priorities of the human beings of each community (A. Elzawawy, 2011). Moreover, we see that the term "personalized" or "customized" cancer treatment is usually concentrated on hitting one or more biological targets that could varied from a tumor to another. We proposed to extend this term to include more aspects of the human host like variability in pharmcogenomics, pharmcodynamics and pharmacokinetics for different drugs, and other personal variations in human beings like socio-economic aspects. Hence, we hope that in the future, the term personalized treatment would pass from "The mechanics" of hitting one target in the tumor by a drug, to the more broader concept and vision of medicine to consider biological tumor factors, human factors and medical wisdom without compromising the overall outcome and via evidence based researches and trials. It is a real challenge. (Elzawawy,2011).

There is a question raised recently in the USA "We have a choice: do we use science to help us reach consensus on what we are willing to pay for new therapies and innovation, or do we leave individual patients to wrestle with the skyrocketing costs of cancer care and treatment determined by their ability to pay?"(Malin, 2010). And globally, we raise the question, are we going to see innovation in cancer treatment and drugs as a of complicating problems of its affordability or we will use science to lessen this rising problem as it facilitates many things in our daily life?.

9. Conclusion

There are no indications that the costs of the novel cancer drugs and radiotherapy of cancer and the incidence and prevalence of cancer will stop increasing in the next decade. Hence, there would be more difficulties and challenges for patients, families, governments, physicians, manufacturers of cancer drugs and radiotherapy equipment, particularly in Low and Middle Income Countries (LMICs). However, there are also increasing concerns in affluent countries and the USA about the increasing costs of cancer therapy. Starting from December 2007, with communications, publications and working meetings, the win-win initiative was proposed by ICEDOC's Experts in Cancer without Borders (ICEDOC: is the International Campaign for Establishment and Development of Oncology Centers www.icedoc.org). The win-win initiative stress on the scientific approaches and in considering stakeholders in win-win scenarios in which no one would lose. Our concerns is to lower the total costs (not necessarily the price of a drug or an equipment), to flourish the system and save it from risk of collapse. In this chapter, we reviewed examples of the recently published scientific works that could lead to lower the overall costs of breast cancer radiotherapy and systemic chemotherapy and hormonal treatment without compromising patients' outcomes. It is presented as a model, to be expanded to other cancers. The cited approaches, with our views, are not presented as wholly inclusive or definitive solutions but are offered as effective examples and as stimuli to hopefully inspire the development of more evidence based management approaches that provide cost effective and more affordable cancer treatment. We recommend to adopt win-win scenarios and to create what Franklin D Roosevelt described as "A Brain Trust" opened for innovative scientific thoughts, ideas and strategies, to foster relevant scientific researches and collaboration that would aim at achieving cost-effective and accessible cancer treatment for more millions of patients with cancers in the world. The win-win initiative is an open movement and it is inspired from the works and publications of many scientists. We don't claim patency. The key leaders of international oncology community and organizations are sharing in the development of the initiative and its working meetings. Hence, it is a concept and an approach that we call all for cooperation for its wide dissemination, to be adopted and to be owned by all who are concerned in the upcoming years. We emphasize on the importance of considering the broad sense for the term science and not to be taken as just to copy the imported protocols or guidelines of treatment. Hence, scientific cooperation, exchange of experiences, customized clinical trials and treatment that respect the realistic biological, human, social and economic conditions, cost -effectiveness, quality of life cost -utility and adapted to each community are recommended. Despite that, the motivation of this initiative is largely humanitarian, but it is based on scientifically derived evidence and reflects 'win-win' scenarios for global cancer management.

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11. References

Anderson, B.O.; Shyyan, R.; Eniu, A.; Smith, R.A.; Yip, C.H.; Bese, N.S.; Chow, L.W.; Masood, S.; Ramsey, S.D. & Carlson, R.W. (2006). Breast cancer in limited resource countries: an overview of the Breast Health Global Initiative 2005 guidelines. *Breast J,* Vol. 12, Jan-Feb 2006, Suppl. 1, pp. S3-15

Anderson, B.O. & Cazap E. (2009). Breast Health Global Initiative (BHGI) outline for program development in Latin America. *Salud Publica Mex,* Vol. 51, Suppl. 2, pp. 309-315, ISSN 0036-3634

Bach, P.B. (2007). Costs of cancer care: a view from the centers for Medicare and Medicaid Services. *J Clin Oncol*, Vol. 25, pp. 187-190

Becker,G.; Hatami,I.; Xander, C.; Dworschak-Flach,B; Olschewski, M; Momm, F; Deibert,P.; Higginson, I.J. & Blum,H.E. (2011). Palliative cancer care: an epidemiologic study. *J Clinc Oncol*, Vol. 29, No. 6, pp. 646-50

Bese, N. S.; Munshi, A.; Budrukkar, A.; Elzawawy, A. & Perez C.A. (2008). Guidelines for International Breast Health and Cancer Control–Implementation. Breast Radiation Therapy Guideline Implementation in Low- and Middle-Income Countries. *Cancer*, Vol. 113, No. 8 Suppl., pp. 2306-13

Bhadrasain, V. (2005). Radiation therapy for the developing countries. *J Can Res Ther*, Vol. 1, pp. 7-8

Centers for Medicare & Medicaid Services. (2007). Proposed decision memo for erythropoiesis stimulating agents (ESAs) for non-renal disease indications (CAG-00383N). Available from: <http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=203&ver=12&NcaName=Erythropoiesis+Stimulating+Agents+&bc=BEAAAAAAEAAA&>

Chadha, M.; Woode, R.; Sillanpaa, J.; Feldman, S.; Boolbol, S.; Furhang, E.; *et al*. (2007). Three-week Accelerated Radiation Therapy (ART) schedule with a concomitant in-field boost as treatment for early stage breast cancer. *Int J Radiat Oncol Biol Phys*, Vol. 69, pp. S137

Chow, E.; Wu, J.; Hoskin, P., *et al.* (2002). International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol*, Vol. 64; pp. 275-280

Chow, E., Harris, K.; Fan, G.; *et al*. (2007). Palliative radiotherapy trials for bone metastases: a systemic review. *J Clin Oncol*, Vol. 25, pp. 1423-1436

Colleoni, M.; Rocca, A.; Sandri, M.T.; Zorzino, L.; Masci, G.; Nole, F.; Peruzzotti, G.; Robertson, C.; Orlando, L.; Cinieri, S.; Viale, G. & Goldhirsch, A. (2002). Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. *Ann Oncol*, Vol. 13, pp. 73–80

Colleoni, M.& Maibach, R. (2007). Breast international group newsletter. 9:,pp 22.

Connolly, R. & Stearns, V. (2009). The role of pharmacogenetics in selection of breast cancer treatment. *Current Breast Cancer Reports,* Vol. 1, pp. 190–197.

Chustecka, Z. (2011). Early Warning System for Prescription Drug Shortages. Available from Medscape Medical News, Oncology: <http://www.medscape.com/viewarticle/737038>

Datta, N. & Rajasekar, D. (2004). Improvement of radiotherapy facilities in developing countries: a three-tier system with a teleradiotherapy network. *Lancet Oncol,* Vol. 5, pp. 695–98

De Souza, J.A. & Bines, J. (2009). The global breast cancer disparity: Strategies for bridging the gap. *JAMA*, Vol. 302, No. 23, pp. 2589-2590

Dowling, R.J.; Goodwin, P.J. & Stambolic, V. (2011). Understanding the benefit of metformin use in cancer treatment. *BMC Med,* Vol. 9, No. 1, 6 April 2011, pp. 33

Drummond, M. & Mason, A. (2009). Rationing new medicines in the UK. *BMJ*, Vol. 338, (22 January 2009), pp. a3182

Early Breast Cancer Trialists' Collaborative Group. (2000). Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. *Lancet*, Vol. 355, pp. 1757-70

Ejlertsen, B.; Mouridsen, H.T.; Jensen, M.B.; Bengtsson, N.O.; Bergh, J.; Cold, S.; *et al*. (2006). Similar efficacy for ovarian ablation compared with cyclophosphamide, methotrexate, and fluorouracil: From a randomized comparison of premenopausal patients with node-positive, hormone receptor-positive breast cancer. *J Clin Oncol*, Vol. 24, pp. 4956-62

Ellis, M.J.; Gao, F.; Dehdashti, F.; Jeffe, D.B.; Marcom, P.K.; Carey, L.A.; Dickler, M.N.; Silverman, P.; Fleming, G.F.; Kommareddy, A.; Jamalabadi-Majidi, S.; Crowder, R.& Siegel, B.A. (2009). Lower-dose vs high-dose oral estradiol therapy of hormone receptor–positive, aromatase inhibitor–resistant advanced breast cancer: A phase 2 randomized study. *JAMA*, Vol. 302, No. 7, pp. 774-780

Elzawawy, A.M.; Elbahaie, A.M.; Dawood, S.M.; Elbahaie, H.M.& Badran, A. (2008). Delay in seeking medical advice and late presentation of female breast cancer patients in most of the world. Could we make changes? The experience of 23 years in Port Said, Egypt. *Breast Care*, Vol.3, pp. 37–41

Elzawawy, A.M. (2008). Breast Cancer Systemic Therapy: The Need for More Economically Sustainable Scientific Strategies in the World. *Breast Care*, Vol. 3, pp. 434–438

Elzawawy, A.M. (2009). The "Win-Win" initiative: a global, scientifically based approach to resource sparing treatment for systemic breast cancer therapy. *World Journal of Surgical Oncology*, Vol. 7, pp. 44

Elzawawy, A.M. (2010). Minutes of The 2nd meeting of the Win-Win Initiative, 6th June, 2010, ASCO 2010 Conference, Chicago, IL, USA. Available from <www.icedoc.org/winwin.htm>

Elzawawy, A.M. (2011). Clinical researches and increasing affordability of cancer treatment in middle-income countries: breast cancer as a research model. ASCO International Clinical Trials Workshop, 6th SEMCO-ASCO conference, Cairo, Egypt, January 27-28, 2011. Available from <www.semco-oncology.info/files/15.1.Interactive%20Discussin-Clin%20res_%20increasing%20affordability%20Ca%20tret_Elzawawy.pdf>

Faden, R.R.; Chalkidou, K.; Appleby, J.; *et al*. (2009). Expensive cancer drugs: A comparison between the United States and the United Kingdom. *Milbank Q*, Vol. 87, pp. 789–819

Fairchild, A. & Stephen, L. (2011). Palliative radiotherapy for bone metastases, In: *Decisions Making in Radiotherapy*, Lu, J.J. & Brady, L.W., pp. 25-42, Springer-Verlag, ISBN: 978-3-642-12462

Ferlay, J.; Shin, H.; Bray, F.; Forman, D.; Mathers, C.& Parkin, D. (2010). GLOBOCAN 2008, Cancer incidence and mortality worldwide: IARC CancerBase No 10. Lyon, France: International Agency for Research on Cancer, 2010. Available from: <http://globocan.iarc.fr>

Fitch, K. & Pyenson, B. (2010). *Cancer patients receiving chemotherapy: Opportunities for better management*. Milliman Inc., New York, USA

Foro, P.; Fontanals, A.; Galceran, J.; *et al*. (2008). Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 Fractions compared with 8 Gy in single fraction. *Radiother Oncol*, Vol. 89, pp. 150-155

Gronwald, J.; Byrski,T.& Huzarski, T. (2009). Neoadjuvant therapy with cisplatin in *BRCA1*-positive breast cancer patients. *J Clin Oncol,* Vol. 27, No.15S, pp. 502

Guttmacher, A.E.& Collins, F.S. (2003). Welcome to the genomic era. *N Engl J Med*, Vol. 349, pp. 996–998

Harford, J.B. (2011). Breast-cancer early detection in low-income and middle-income countries: do what you can versus one size fits all. *Lancet Oncol,* Vol. 12, pp. 306–12

Hayman, J.; Weeks, J. & Mauch, P. (1996). Economic Analyses in health care: An introduction to the methodology with an emphasis to radiation therapy. *Int J Radiat Oncol Biol Phys*, Vol. 35, pp.827-841

Himmelstein, D.U.; Thorne, D.; Warren, E.; *et al*. (2009). Medical bankruptcy in the United States, 2007: Results of a national study. *Am J Med*, Vol. 122, pp. 741–746

Hutton, J.; McGrath, C.; Frybourg, J.; *et al*. (2006). Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies (fourth hurdle systems). *Int J Technol Assess Health Care,* Vol. 22, pp. 10–18

Jagsi, R.; Abrahamse, P.; Morrow, M.; Hawley, S.T.; Griggs, J.J.; Graff, J.J.; Hamilton, A.S.& Katz, S.J. (2010). Patterns and Correlates of Adjuvant Radiotherapy Receipt After Lumpectomy and After Mastectomy for Breast Cancer. *J Clin Oncol*, Vol. 28, No. 14, pp. 2396-2403

Jalali, R.; Singh, S.& Budrukkar, A. (2007). Techniques of tumour bed boost irradiation in breast conserving therapy: Current evidence and suggested guidelines. *Acta Oncol* Vol. 46, pp. 879-92

Janjan, N.; Lutz, S.; Bedwinek, J.; *et al*. (2009). Therapeutic guidelines for the treatment of bone metastasis: A report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. *J Palliat Med*, Vol. 12, pp. 417-423

Joensuu, H.; Bono, P.; Kataja, V.; Alanko, T.; Kokko, R.; Asola, R.; Utriainen, T.; Turpeenniemi-Hujanen, T.; Jyrkkiö, S.; Möykkynen, K.; Helle, L.; Ingalsuo, S.; Pajunen, M.; Huusko, M.; Salminen, T.; Auvinen, P.; Leinonen, H.; Leinonen, M.; Isola, J. & Kellokumpu-Lehtinen, P.L. (2009). Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol*, Vol. 27, No. 34, pp. 5685-92

Kaasa, S.; Brenne, E.; Lund, J.-A.; *et al*. (2006). Prospective randomized multicentre trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases. *Radiol Oncol,* Vol. 79, pp.278-284

Khaled, H.; Emara, M.E.; Gaafar, R.M.; Mansour, O.; Abdel Warith, A.; Zaghloul, M.S.; El Malt, O. (2008). Primary chemotherapy with low-dose prolonged infusion gemcitabine and cisplatin in patients with bladder cancer: A Phase II trial. *Urol Oncol*, Vol. 26, No. 2, pp. 133–6

Klotz,L; O'Callaghan,C.J; Ding, K;, D; Dearnaley P; C. S. Higano, C.S; E. M. Horwitz, E.M;

Malone, S;. Goldenberg,S.L;, M. K. Gospodarowicz, M.K; Crook,J.M. (2011). A phase III randomized trial comparing intermittent versus continuous androgen suppression for patients with PSA progression after radical therapy *J Clin Oncol; 29* suppl 7, abstr 3

Kolodziej, M.A. (2011). Does Evidence-Based Medicine Really Reduce Costs? *Oncology*, Vol. 25, No. 3, Available from <http://www.cancernetwork.com/practice/content/article/10165/1821731?GUID=FB148439-5EF7-471B-8A2A-46E108E67287&rememberme=1&source=NL>

Lash, T.L.; Lien, E.A.; Sorensen, H.T. & Hamilton-Dutoit, S. (2009). Genotype-guided tamoxifen therapy: time to pause for reflection? *Lancet Oncol*, Vol. 10, pp. 825–833

Malin, J.L. (2010). Wrestling with the high price of cancer care: should control costs by individuals 'ability to pay or society wildlings to pay? *J Clin Oncol*, Vol. 28, pp. 3212-3214

Meropol, N.J. & Schulman, K.A. (2007). Cost of cancer care: issues and implications. *J Clin Oncol*, Vol. 25, pp. 180-186

Meropol, N.J.; Schrag, D.; Smith, T.J.; *et al*. (2009). American Society of Clinical Oncology guidance statement: The cost of cancer care. *J Clin Oncol*, Vol. 27, pp. 3868–3874

Mileshkin, L.; Schofield, P.E.; Jefford M.; *et al*. (2009). To tell or not to tell: The community wants to know about expensive anticancer drugs as a potential treatment option. *J Clin Oncol*. Vol. 27, pp. 5830–5837

Mitsumori, M. & Hiraoka, M. (2008). Current status of accelerated partial breast irradiation. *Breast Cancer,* Vol. 15, No. 1, pp. 101-7

Munshi, A. (2007). Breast cancer radiotherapy and cardiac risk: The 15-year paradox. *J Cancer Res Ther*, Vol. 3, pp. 190-2

Munshi, A. (2009). Resource-sparing and cost-effective strategies in current management of breast cancer. *J Can Res Ther*, Vol. 5, pp. 116-20

Neubauer, M.A.; Hoverman, J.R.; Kolodziej, M.; *et al*. (2010). Cost effectiveness of evidence-based treatment guidelines for the treatment of non–small-cell lung cancer in the community setting. *J Oncol Pract,* Vol. 6, pp. 12-18

Overgaard, J.; Mohanti, B.; Bhasker, S.; Begum, N.; Ali, R., Agarwal, J.; Kuddu, M.; Baeza, M.; Vikram, B. & Grau, C. (2006). Accelerated versus conventional fractionated radiotherapy in squamous cell carcinoma of head and neck. A randomized international multicentere trial with 908 patients conducted by the IAEA-ACC study group. *Int J Radiat Oncol Biol Phys.*, Vol. 66, No. 3, Suppl., pp. S13

Paik, S.; Taniyama, Y. & Geyer C.E. Jr. (2008). Anthracyclines in the treatment of HER2-negative breast cancer. *J Natl Cancer Inst*, Vol. 100, pp. 2-4

Phillips, K.A.; Marshall, D.A.; Haas, J.S.; *et al*. (2009). Clinical practice patterns and cost effectiveness of human epidermal growth receptor 2 testing strategies in breast cancer patients. *Cancer,* Vol. 115, No. 22, pp. 5166-5174

Porter, A.; Aref, A.; Chodounsky, Z.; Elzawawy, A.; Manatrakul, N.; Ngoma, T.; Orton, C.; Van't Hooft, E.& Sikora, K. (1999). A global strategy for radiotherapy: A WHO consultation. *Clin Oncol (R Coll Radiol)*, Vol. 9, No. 11, pp. 368–370.

Punglia, R.S.; Winer, E.P.; Weeks, J.C. & Burstein, H.J. (2007). Could treatment with tamoxifen be superior to aromatase inhibitors in early-stage breast cancer after pharmacogenomic testing? A modeling analysis. *J Clin Oncol*, Vol. 25, pp. 502

Ratain, M.J. & Cohen, E.E. (2007). The value meal: how to save $1,700 per month or more on lapatinib. *J Clin Oncol,* Vol. 25, pp. 3397–3398.

Sachs, D.L.; Kang, S.; Hammerberg, C.; Helfrich, Y.; Karimipour, D.; Orringer, J.; Johnson, T.; Hamilton, T.A.; Fisher, G.& Voorhees, J. (2009). Topical Fluorouracil for Actinic Keratoses and Photoaging. A Clinical and Molecular Analysis. *Arch Dermatol,* Vol. 45, No. 6, pp. 659-666.

Sarin, R. (2005). Partial-breast treatment for early breast cancer: emergence of a new paradigm. *Nat Clin Pract Oncol*, Vol. 2, No. 1, pp. 40-7

Sarrazin, D.; Le, M.; Arriagada, R.; Contesso, G.; Fontaine, F.; Spielman, M.; Rochar, F.; Le Chevalier, T.H. & La Cour, J. (1989). Ten Year results of randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncolol*, Vol. 14, pp. 177

Schrag, D. & Hanger, M. (2007). Medical oncologists' views on communicating with patients about chemotherapy costs: A pilot survey. *J Clin Oncol*, Vol. 25, pp.233–237

Schrag, D. (2004). The price tag on progress -- chemotherapy for colorectal cancer. *N Engl J Med*, Vol. 351, pp. 317-319

Stewart, B.W. & Kleihues, P. (2003). World Cancer Report. IARC Press, Lyon, France

Sullivan, S.D.; Watkins, J.; Sweet, B.; *et al*. (2009). Health technology assessment in health-care decisions in the United States. *Val Health*, Vol. 12, Suppl. 2, pp. S39–S44

The START Trialists' Group. (2008). The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet,* Vol. 29, No. 371, pp. 1098–1107

Torres Edejer, T.T.; Baltussen, R.; Adam, T.; *et al*. (2003). Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization, Geneva, Switzerland

Truong, P.T.; Olivotto, I.A.; Whelan, T.J.& Levine, M. (2004). Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy. *CMAJ,* Vol. 170, No. 8, pp. 1261–1273

Van den Hout,W.B.;Van der Linden, Y.M.; Steenland, E.;Wiggenraad, R.G.; Kievit, J.; de Haes, H. & Leer, J.W. (2003). Single-Versus Multiple-Fraction Radiotherapy in Patients with Painful Bone Metastases: Cost-Utility Analysis Based on a Randomized Trial. *Journal of the National Cancer Institute,* Vol. 95, No. 3, pp. 222–29.

Weeks, J. C. (2003). Outcomes Assessment, In: *Cancer Medicine*, Kuff, D.W., Pollok, R.E., Weichselbaum, R.R., Bast, R.C., Gansler, T.S., Holland, J.F., Frei, E, pp. 479 -502, BC Decker Inc., ISBN 1-55009-213-8, Hamilton-London.

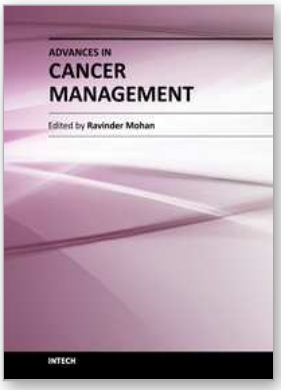
Wennberg, J.E.; Fisher, E.S.; Goodman, D.C. & Skinner, J.S. (2008). Tracking the care of patients with severe chronic illness. In: Dartmouth Institute for Health Policy and Clinical Practice. The Dartmouth atlas of health care 2008. Available from <http://www.dartmouthatlas.org/downloads/atlases/2008_Chronic_Care_Atlas.pdf>

WHO, World Health Statistics 2010. France: World Health Organization, Department of Health Statistics and Informatics of the Information, Evidence and Research Cluster, 2010.

Yarney, J.; Vanderpuye, V.& Clegg Lamptey, J.N. (2008). Hormone receptor and HER-2 expression in breast cancers among Sub-Saharan African women. *Breast J*, Vol. 14, pp. 510–511

Yip, C.H.; Cazap, E.; Anderson, B.O.; Bright, K.L.; Caleffi, M.; Cardoso, F.; Elzawawy, A.M.; Harford, J.B.; Krygier, G.D.; Masood, S.; Murillo, R.; Muse, I.M.; Otero, I.V.; Passman, L.J.; Santini, L.A.; da Silva, R.C.; Thomas, D.B.; Torres, S.; Zheng, Y.& Khaled, H.M. (2011).Breast cancer management in middle-resource countries (MRCs): consensus statement from the Breast Health Global Initiative. *Breast,* Suppl 2, pp. S12-9.

Zwitter, M.; Kovac, V.; Smrdel, U.; Kocijancic, I.; Segedin, B. & Vrankar, M. (2005). Phase I–II trial of low-dose gemcitabine in prolonged infusion and cisplatin for advanced non-small cell lung cancer. *Anticancer Drugs,* Vol. 16, pp. 1129–1134.



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Cancer is now the most common cause of death in the world. However, because of early diagnosis, better treatment, and advanced life expectancy, many cancer patients frequently live a long, happy, and healthy life after the diagnosis- and often live as long as patients who eventually do not die because of cancer. This book presents newer advances in diagnosis and treatment of specific cancers, an evidence-based and realistic approach to the selection of cancer treatment, and cutting-edge laboratory developments such as the use of the MALDI technique and computational methods that can be used to detect newer protein biomarkers of cancers in diagnosis and to evaluate the success of treatment.

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