

Efficacy of Oncologic Drug therapy: Some to Rethink in the Management of the System?

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Short Communication

Healthcare management today more than past need strong condition in using drugs resource in oncology filed. Cancer is so diffused and elderly people are increasing in modern society. The economic resource involved in this condition is increasing in logarithmic way. Every medical discipline has disease treated with high or medium or low results so in the same way we can have drugs with different profile of efficacy. We can observe that many diseases have efficient drug therapy, often only one drug resolve the pathological condition. In order to have more clinical results, combination of drugs are used, (for example initially Sulfametoxazole-trimetoprim was used in antimicrobial filed) but in many disease even with the combination of 4 drugs the percentage of disease cured doesn't increase. What does it mean? For example we can see in many oncologic diseases or in metabolic disorders (such as type 2 diabetes) they are currently using combination of drugs to improve clinical outcome. It means that these drugs are not the best or low active? Why for these pathological conditions, drugs not do the work? There is a need for new efficient drugs that show a profile of efficacy as requested in order to resolve the pathological condition? Is it ethical to approve and register new oncological drugs that demonstrate 1-2 months in surviving? Is it ethical that public institution pay for drugs that increase only few months surviving? The economic aspect is relevant on cost of drugs and payment by government and institution or insurance (example 30-40.000 euro/USD/patient for some biological MABS). Even ministry of health in some countries (example Italy), not only pay for all new innovative anticancer drugs but use a system that verify the results obtained (payment by results, risk sharing etc. other procedure). There are a medical procedure currently used in healthcare that has 100% of efficacy (for example in sterilization of medical devices or parenteral drugs) but we have registered a lot of drugs with high variable profile of activity. Other drugs show real efficacy for example: acetyl salicylic acid in anti-aggregate properties. The same morphine has its own analgesic property and often not need in combination to other drug classes to have a good level of activity [1]. The same for chloramphenicol, we know its efficacy even if we know well its toxicity. Statins are used in lowering cholesterol, thiopental in ICU, heparin and many others example such as insulin, some antidotes, and some anesthetic or muscle relaxant molecules. In neuropsychiatric disease drugs show a variety of efficacy and a great placebo effect (in some cases about 30%). In some conditions we can see for example in the treatment of type II diabetes, we see a great use in poly therapy, association are commonly used in antimicrobial therapy in MDR resistance and other factors [2]. For example, Clavulanic acid is used as enzymatic inhibitor in combination with Amoxicilin and other drugs used for TBC infections (triple therapy) or for HIV to reduce resistance.

But also in oncologic field we can see a great use of multidrug therapy (even if there are neoplastic with great response to drugs in other we do not have a good response). What is the meaning of this situation? Do we have today the right efficacy drugs? Or we have to think to a new generation of drugs that prove real and relevant clinical efficacy to be used with real useful results? In oncologic field we have

today sophisticated biological agents registered, that shows efficacy in short period? Is it the right strategy to use the limited economic resource? Is it really the best option to register drugs that gives only few increase or not relevant in mortality rate or other hard endpoint? Why commonly used drugs show high level of resistance (for example simple use of different intracellular second massager)? This situation easily gives resistance. Why is it used to poison the cell with some intracellular oncology drugs when it is known that the cell naturally extrude poison from its inside as a natural defense mechanism? The introduction of novel delivery systems that make possible to bypass this problem can give more clinical results [3]. The classic chemotherapy drugs must act in cancer cell in priority way and new delivery systems can do it in better way. The cancer cell during its life has different and progressive mutation and in some cases the drugs used give mutation itself. In some cases of cancer to pancreas, liver, brain, gastric their response to chemotherapy is not at level of treatment of other (LMC agents) and this is a real key point to rethink the problem. Hematologic cancer has a different profile of drugs response vs. solid tumors. We cannot use the term healing in oncology field in light way. Because reactivation of disease can be seen after certain period and clinical healing cannot be a molecular complete response. It is easy to think that the chronic patients are more interesting vs. a get better one (can be a pharmaceutical industries view). In the last decades we have seen a progressive improvement of anticancer therapy using different strategies as association of chemotherapy, tirosin kinase inibithors, mabs, radiodrugs and other.

Cycle of chemotherapy associated to mabs can attack the cancer cell in different stages or with different mechanism. Continuous infusion of some chemotherapy drugs increase activity in example (cell are in different cycle). Using cycle strategy toxicity can be contained and efficacy improved. If classic chemotherapy drugs are associated with different level of toxicity using mabs we should have this kind of problems and the possibility to treat elderly patient or in severe conditions. The knowledge in genetic profile, mutation level can gives the right therapy application and not using towards patient for example genetically resistance [4]. Mutation, genetic instability and other condition can heavily influence the drug therapy response. The increase of clone resistance is easily in tumor destiny. The presence of sanctuary for metastatic cell contributes to the evolution of the pathology. Other tumor can be kinetically resistance because high part of the cell remains

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Received July 23, 2016; **Accepted** February 13, 2017; **Published** February 16, 2017

Citation: Luisetto M (2017) Efficacy of Oncologic Drug therapy: Some to Rethink in the Management of the System? Int J Econ Manag Sci 6: 399. doi: [10.4172/2162-6359.1000399](https://doi.org/10.4172/2162-6359.1000399)

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in a cycle face characterized by low rate of development (for this reason the association of different drugs with different profile of action gives more results vs. immunotherapy).

Other causes of resistance can reduce permeability of the cancer cell to the chemotherapy drugs.

Augmented metabolism of the drugs, augmented extrusion from cell inside (extrusion pump), Enzyme level augmented in response to the inhibitor drugs used, Alternatives pathways enzymatic deficit due to the drug activity, Gene amplification, Alternated metabolism, augmented inactivation, alternated DNA reparation system, Target modify, receptor internalization, Alternative subway mechanism, Drug intake modified, Lower cellular intake of drugs, Anti-apoptotic mechanism, Pletotropic resistance (towards different class of molecules), MDR, and other relevant mechanisms.

Classic chemotherapy drugs present high toxicity bus vs. mabs show less resistance linked to the direct toxicity. However only few mabs show a real efficacy (HERCEPTIN RITUXIMA CETUXIMAB BEVACIZUMAB and few others) and many present resistance profile. We have few mabs in first line vs. classic chemotherapy drugs association using nanotechnologies we can lead classic drugs into the only cancer cell bypassing the resistance in example in mabs therapy.

But thinking at the actual situation: We need new rules for registered clinical trial? And why it is demonstrated the clinical pharmacist in medical team we have general improvement in clinical outcome is not officially required this presence in registered clinical trial?

The decision making systems in cancer therapy must consider the clinical pharmacist presence in the medical team to improve clinical outcomes:

“Every drug is registered for specific indication, at the same time every drug to be a rational therapy should need a rational decision making system that require a multidisciplinary team that can cover all aspect of pharmaceutical molecular metabolism kinetics and pharmacodynamics this create great possibility for clinical pharmacist but it must increase expertise in field of diagnostic (lab medicine and imaging) for the high relationship whit drug therapy”

“Is a clinical pharmacist is required in the presence of a clinical trial for drug registered use? If the pharmacist presence in medical team gives improving clinical outcomes, why is it not requested by regulatory clinical pharmacist presence in registered trial?” in clinical trials today used vs. gold standard PFS progression free survival, overall survival, TTP, TTF, EFS, TTNT, ORR, DOR to compare activity.

We observed some publication in biomedical database, Luisetto et al. [5] observed general improvement in some clinical outcomes when clinical pharmacist take really part of medical team. The classical model for identification and clinical development of anticancer agents was based on small molecules, which were often quite toxic. The decision to take the drug into the randomized phase III clinical setting was usually based on the proportion and duration of objective tumor responses, along with overall survival compared with historical controls.

Immune-oncologic that are designed to fight cancer by direct CD8(+) T-cell priming and activation or by blocking a negative regulatory molecule have a number of sharp distinctions from cytotoxic drugs. These include cyto-reductive effects that may be very different in timing of onset from traditional chemotherapy and the potential for inducing long-term durable remissions even in heavily pretreated patients with metastatic disease [6]. In this paper we review the

different classes of immune-oncologic drugs in clinical development with particular attention to the bio statistical challenges associated with evaluating efficacy in clinical trials. Confronting these issues upfront is particularly important given the rapidly expanding number of clinical trials with both monotherapy and combination trials in immune oncology.

As with other medical drugs, the marketing authorization decision is based on the assessment of its efficacy, safety and pharmaceutical quality but does not consider price or reimbursement. More sophisticated diagnostic methods drive an increasing stratification of cancer into a multitude of different diseases. Regardless of their different pathogenesis and therapeutic options the most relevant clinical endpoints remain cure, overall survival and progression free survival. These endpoints include both efficacy and safety, as patient survival reflects the sum of the beneficial anti-tumor effects (increasing survival) AND the adverse effects (decreasing survival) [7]. The benefit of an anticancer medicine should be evident from both overall survival and progression free survival (e.g. used as primary and secondary endpoints). Mature data on overall survival may not be needed for marketing authorization if a clear increase in progression free survival convincingly predicts a beneficial effect on overall survival. In these exceptional cases treatment of patients with an obviously beneficial medicine must not be delayed - possibly for years - until the exact size of the benefit has been established. Conditional approval and approval under exceptional circumstances may accelerate patients' access to a new medicine. Both postulate that the extent of the benefit cannot be determined with sufficient certainty at the time of marketing authorization. This uncertainty may have a negative impact on price and reimbursement as these decisions may consider data or assessments from the marketing authorization procedure [8]. Therefore, marketing authorization applications and subsequent pricing and reimbursement negotiations should not be regarded as completely independent processes, but be included in an overall strategy for the development of oncologic drugs.

Present Status and Problems on Molecular Targeted Therapy of Cancer

Numerous clinical trials of molecular targeted drugs for cancer have been conducted, with remarkable results for certain drugs and accumulation of "negative data" causing a hitch in the development plan for some other compounds. Drug discovery and effects against driving mutations (activating mutations) and problems: possibility for circumventing inherent and acquired resistance with the aim of achieving radical cure. Synthetic lethality: reasonable patient selection in individualized treatment strategy. Response rate and progression-free survival improvement with or without overall survival benefit and enhancement of toxicity in bevacizumab therapy are the best endpoints for evaluation of effect of anti-angiogenic therapy. Negative data on small-molecule targeted therapy, primarily vascular endothelial growth factor tyrosine kinase inhibitors: loose GO or NO-GO decision criteria for further development of new compounds in early clinical trials. Effect of monotherapy is difficult to verify by proof of principle study. We faced so many questions for the development of efficient personalized therapy. Accumulation of scientific global preclinical and clinical evidences is essential for the use of these new therapeutic modalities for the improvement of oncologic health care. Although improved survival is the "gold standard" for proving clinical benefit of oncologic therapy, the U.S. Food and Drug Administration (FDA) has accepted significant results in clinical trials using surrogate endpoints

as the basis for drug approval. One surrogate method is the amount of tumor reduction, or tumor response. Moreover, tumor response may not be an appropriate endpoint for evaluating the effects of the new targeted therapies, whose putative mechanisms are generally cytostatic rather than cytotoxic. Clinical trials suggest that some patients with other solid tumors, such as lung cancer, may derive clinical benefit from treatment that helps stabilize their disease. There is also controversy as to whether the Response Evaluation Criteria in Solid Tumors (RECIST) provides the most appropriate instrument for assessing tumor burden. Ultimately, use of a variety of endpoints as well as different trial designs may provide an adequate basis for investigation of the benefits/risks of newer therapies. "Every drug is registered for specific indication, at the same time every drug to be a rational therapy need a rational decision making system that require a multidisciplinary team that can cover all aspects of pharmaceutical molecular metabolism kinetics and pharmacodynamics, this create great possibility for clinical pharmacists; but it must increase expertise in field of diagnostics (lab medicine and imaging) for the high relationship with drug therapy. The old algorithm was "physicians - patients - classic pharmacist".

"We submit to the scientific community "Clinical Pharmaceutical Care" as a new discipline. Discipline intended to improve clinical and economic endpoint in pharmacological therapy reducing therapy errors and with a more rational application of resource in medical team (clinical pharmacist). This new approach takes advantages using the Management and ICT principles. We ask also to international organization involved in hospitals accreditation and University to recognize this new health care professional activity. We think that core training must include principles of Management, ICT Professional social media, psychological behavior skills for team working added to be added to the classic clinical pharmacy programs.

Theory and Practical Applications

Also the knowledge in field of medical laboratory and imaging give great advantages in this new discipline for the hard relationship with many drug therapies. For this reason also clinical pharmacist must be involved. We strongly ask to public institution to apply this new discipline to obtain more rational drug"

Discussion/Conclusion

Under the light of this results found in actual situation we can

say that today it is essential to evaluate efficacy of drugs in registered protocols. This in order to have drugs with relevant profile of efficacy and a systems that allow to differentiate the molecule only for research study (with low activity profile that justify the use in therapy) from the real efficacy molecule to apply in therapy. The question is we need new anticancer drugs that improve the clinical outcomes or do we need to have a new heavy process to register the new drugs? We need other drugs copy or do we need new pharmaceutical mechanism for anticancer treatment? Who must pay for copy drugs with little improvement in clinical outcomes? We don't say that is wrong use the actual drugs registered for neoplastic treatment in the cycle and protocols approved (in example gold standard) but we say only that in registering process is necessary for new drugs that the real relevant efficacy is verified to justify the current use in therapy and the cost involved.

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Citation: Naqvi A, Naqvi F (2017) A Study on Learning Styles, Gender and Academic Performance of Post Graduate Management Students in India. Int J Econ Manag Sci 6: 399. doi: 10.4172/2162-6359.1000399

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