ARC Journal of Dental Science
Volume 3, Issue 3, 2018, PP 11-17
ISSN No. (Online) 2456-0030
DOI: http://dx.doi.org/10.20431/2456-0030.0303004
www.arcjournals.org

The Other Side of Oral Anti-Cancer Agents: Boon or Disguise

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Abstract: *The global prevalence of cancer is rising. Use of oral anticancer medications has expanded exponentially. Knowledge about these medications as well as safe handling guidelines has not kept abreast with the rapidity these medications are applied in clinical practice. They pose serious hazards on all personal involved in handling these medications as well as on patients and their caregivers. The use of oral anticancer agents increased steadily in the last decades. Although oral anticancer agent adherence is important for a successful treatment, many patients are insufficiently adherent and controversies regarding the oral side effects or adverse events associated with targeted cancer therapy. Common oral toxicities include the terms mucositis, stomatitis, dysphagia, xerostomia, pharyngitis, and taste alterations. The use of oral anticancer agents has increased in the last decades. Adherence is a crucial factor for the success of oral anticancer agent therapy. However, many patients are non-adherent. The significance of oral delivery in cancer therapeutics has been highlighted which principally includes improvement in quality of life of patients and reduced health care costs. Subsequently, the challenges incurred in the oral delivery of anticancer agents have been especially emphasized. Sincere efforts have been made to compile the various physicochemical properties of anticancer drugs.*

Keywords: *squamous cell carcinoma, Oral anticancer agents, Oral chemotherapy, Oral delivery, Anticancer activity*

1. Introduction

The cancer burden is rising in many developing countries. It is projected that cancer incidence will increase from 12.7 million in 2008 to 22.2 million by 2030 [1]. The first oral anti-cancer chemotherapy dates back to the 1940's of the last century. The therapeutic use of Nitrogen Mustard for certain haematological malignancies was first reported by Goodman et al. [2]. With the increasing understanding of cancer biology and molecular genetics a variety of Oral Anti-Cancer Agents (OAAs) are developed targeting key cellular mechanisms involved in tumour resistance to conventional therapies. It is estimated that 25% of all targeted anticancer agents will be oral medications and more than 400 oral agents are in the development pipeline [3]. They are used as single agents or in combinations to treat a variety of different cancers. In the last decades a tremendous expansion in the indications of OAAs has taken place in solid tumours and haematological malignancies [4].

Treatment options for HNC consist of radiotherapy, surgery, chemotherapy or a combination of these modalities. There is a growing body of evidence suggesting that more aggressive treatment regimes, such as altered fractionation schedules for radiotherapy or (concomitant) chemo radiation improve tumor control and survival [5-7]. Recent meta-analyses showed absolute improvements in 5-year survival of 3% for altered fractionation versus conventional fractionation and of 5% for chemotherapy versus no chemotherapy [7, 8]. However, mainly due to the close proximity of critical organs and the often large irradiation fields, the improved outcomes in these aggressive treatment regimes come at the cost of increased treatment toxicity. Late toxicities (including xerostomia and dysphagia) affect a substantial proportion of HNC patients and negatively affect patients' functional outcomes and quality of life [9].

2. Delivery of Anticancer Drugs

Chemotherapy is one of the most widely utilised procedures for treating cancer [10]. Despite its many merits, the application of this treatment is limited by severe toxic side effects of anticancer drugs on healthy tissues [11, 12]. Efforts are

being made to tackle this issue by developing more benign drugs [13]. Recent reports, however, show that it is also possible to overcome this challenge by exploiting the potential of local drug delivery systems (DDS) for the deployment of anticancer agents [14]. The highlight of a localised DDS approach is the possibility of implanting drug-releasing devices directly at the tumour site. Proceeding this way, it is possible to minimise both systemic exposure and side effects of chemotherapy [15]. Several approaches to the development of such systems have heretofore been reported, utilising chitin microparticles [16], biodegradable polymeric microspheres [17], poly (D, L-lactide-co-glycolide) wafers [18], poly [bis (p-carboxyphenoxy) propane-sebacic acid] copolymer discs [19] as well as other, intravenous delivery systems, based on nanoparticles and polymers [20, 21]. All of the above share a common mechanism of drug delivery – the spontaneous release of bioactive molecules from the matrix upon its bio-assisted decomposition. Conjugated polymers, possessing ion-exchange properties, are considered promising materials for use as drug reservoirs in drug delivery systems [22]. In contrast to the physical entrapment [23], conjugated polymers allow controlled, reversible electrostatic immobilisation. The mechanism of this process relies on the fact that conducting polymers, depending on their oxidation state, undergo a charging–discharging process and adopt positive or negative charges.

These charges draw ions of opposite charge into the polymeric matrix, binding them via Coulomb interactions. Therefore, they are able to immobilise anionic drugs during oxidation (doping) and release them in the process of reduction (dedoping). The controlled immobilisation/release mechanism is highly desired, however, the development of implantable drug delivery systems necessitates all of the device constituents to be fully biocompatible. Although biocompatibility is not inherent to conjugated polymers, some among them, such as polypyrrole [24] and poly (3, 4-ethylenedioxythiophene) (PEDOT) [25], exhibit this trait.

The use of oral anticancer therapy affects many clinically relevant aspects such as the following [26]:

1. An appropriate plasma drug concentration can be maintained to achieve a prolonged exposure of drugs to cancerous cells. This will increase the efficacy and decrease the side effects of the anticancer drugs.
2. Modulation of drug release from the dosage forms also provides an added advantage compared to that in other routes of administration.
3. It further facilitates the use of more chronic treatment regimens. This is especially important for cell cycle specific agents, especially those of predominantly cytostatic effect such as angiogenesis inhibitors and signal transduction inhibitors. For these agents, prolonged exposure to the drug may lead to pharmacodynamic advantages over intermittent intravenous administration.
4. Oral chemotherapy avoids the discomfort of injection and can be conducted at home. This approach may enhance the patient cooperation and their quality of life, which is an important issue and thus deserves high attention for any medical treatment.
5. The risks of infection and extravasations associated with intravenous infusion lines are avoided.
6. The treatment cost for the patient can be highly reduced due to avoidance of hospitalization, sterile manufacturing and trained personnel assistance.
7. Apart from the therapeutic applications, oral therapy can also be explored in the segment of prophylactics due to high level of ease in administration.

3. COMPLICATIONS

Conventional cancer chemotherapeutics carry a heavy toxicity burden. Oral side effects include mucositis, hyposalivation/ xerostomia, dysphagia, pharyngitis, infection, discomfort, and taste alterations. Mucositis has been reported to affect many patients receiving high dose conventional chemotherapy [27]. The common clinical presentation of cytotoxic chemotherapy mucositis includes painful inflammation, erythema, and ulcerations of the oral mucosa and digestive tract. As cancer treatment protocols evolve, emphasis is placed on developing therapies specific to neoplastic tissue to eradicate or control malignancies while maintaining minimal toxicities affecting non-neoplastic tissue. Molecularly targeted cancer therapies have been developed that block the growth and survival of cancer cells by interfering with specific molecules and pathways involved in carcinogenesis. These treatments include anti-

tumor monoclonal antibodies (mAbs), small molecules, signal transduction receptor inhibitors, and cancer vaccines. Targeted cancer therapies are indicated in the first and second line treatment of a variety of solid tumors of varying stages including: lung, breast, kidney, colorectal, head and neck, and hematopoietic malignancies [28-30]. Published studies investigating the safety of targeted therapies have indicated that fewer oral complications are experienced with these agents. Reports to date focus on acute complications with limited information published on chronic complications and survivorship issues.

The side effects from targeted cancer therapies are considered to be mild to moderate, and in most cases substantially less than conventional cancer chemotherapy [31]. If targeted therapies are combined with conventional cancer therapies previously identified toxicities may be increased in severity or duration. Additionally, adverse events that were unexpected in the preclinical setting may occur [32]. Oral manifestations of targeted therapies may be independent or additive to oral complications in radiation and conventional chemotherapy. Oral mucositis may present with broad areas of erythema, aphthous-like stomatitis, or compound mucositis associated with conventional therapy [33]. While some molecules have overlapping mechanisms of action and may affect different parts of the same pathway, thus having similar cellular effects, their side effect profiles may differ. Other molecules target multiple pathways and as such have unique molecular signaling effects and side effects.

4. Adherence Influencing Factors in Patients Taking Oral Anticancer Agents

The use of oral anticancer agents (OACA) has increased steadily. One quarter of newly developed anticancer agents can be taken orally [34]. The use of OACA will probably increase further. Most patients prefer to take their medication orally [35]. Adherence, defined as ‘‘the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen’’ [36] is lower in patients taking OACA compared to patients treated with intravenous chemotherapy [37]. It is estimated that adherence rates in patients taking OACA lie in a range between less than 20% and 100%, depending on patient characteristics, therapy and adherence measurement and definition [38, 39]. For some cancer types adherence to OACA turns out to be crucial factor for the success of treatment [40-42], especially given the long period in which OACA have to be taken correctly. Consequently, adherence has become a key issue in modern oncology treatment. There are several factors that can potentially influence patient adherence [43]. In clinical practice the knowledge about factors that influence patient adherence can help to identify patients at risk for non-adherence and also help to develop methods to improve adherence in affected populations.

However, several factors (patient characteristics, treatment characteristics, disease characteristics, setting) exist, for which an influence on patient adherence in patients taking OACA has been shown [44]. The factors can be roughly divided in the following five dimensions: Social and economic, health care system, health condition, therapy and patient [45].

Social and economic factors are all factors concerning the social an economic status of a person. For example, poverty and income can result in conflicting priority-setting regarding the use of limited resources. The consequence can be that adherence is reduced because the priority for other demands than medications (e.g., food) is perceived higher.

Health care system factors are all factors that relate to the organizational structures of the health care system/services and characteristics of the health care professionals. This includes e.g., the coverage of health insurance, patient-provider relationship or medication distribution.

Age, ethnic status, social support, depression, intake of aromatase inhibitors, number of different medications, and out-of-pocket costs seem to have an effect on adherence. The remaining factors either showed mostly no influence or a clear conclusion is not possible, because the results differed between studies. Due to the heterogeneity no general conclusions for all factors, – also for those emphasized above can be made that can be applied to all indications, medications, settings, countries etc. The results should rather be considered as indications for factors that can have an influence on adherence to OACA. To be of sufficient significance to make decisions in clinical practice, the factor/s has/ has to be evaluated in detail for the specific context of the decision. The main reasons for heterogeneity between studies are the sample size, the analyses methods, different OACA and different tumor types. Adherence to OACA in breast cancer treatment was the most frequent analyzed indication. But the results remain

heterogeneous when exclusively focusing on this subgroup of patients. Also the differences in health care systems can cause heterogeneity.

Adherence is operationalized in two ways, either as the mean of the whole study sample or as the proportion of adherent patients. The advantage of using a continuous adherence operationalization in the analysis of influencing factors as dependent is that it allows a judgment on which factors could affect adherence ''in general''. Prior research has shown that the categorization of variables can result in different predictors in prognostic models and poor performance of the model. Mean adherence is only used to operationalize adherence in six studies and is probably one reason for different results regarding the statistically significance and effect direction of the same factor in different studies [40, 45-47]. The mean adherence allows no quantification of patients that did not reach the required adherence. To have a substantial therapy effect, patients have to reach a certain adherence level. Taking this into account, the proportion of patients reaching this adherence level is necessary to estimate the prevalence of clinically meaningful non-adherence. Unfortunately, to our knowledge, a precise lower bound of required adherence (dose and timing) has not been proven for any OACA, yet. Research is needed to determine the level of adherence needed to reach a substantial clinical effect for different OACA to determine a quantification of patients which are non-adherent.

Theoretically, it is imaginable as with screening to identify patients with a low baseline adherence with a validated measurement tool. However, in practice this is difficult, because patients must be observed before starting therapy and over a certain period. Knowledge on risk factors for non-adherence can help to identify non-adherent patients in clinical practice, in particular for patients starting a treatment [48]. Furthermore, the knowledge on adherence influencing factors can contribute to the development of risk factor based screening tools. Similar instruments have been developed for other indications [49]. Prior research has shown that existing adherence enhancing interventions are mostly less effective [50]. The knowledge on adherence influencing factors could support the development of interventions that are tailored to specific patient needs. It is unlikely that adherence is influenced by only one factor but rather a multifactorial phenomenon [43]. The question which factor combinations affect adherence remains unanswered in this analysis. Further research is needed to gain an insight into critical and positive factor combinations.

5. Safety of Oral Anti-Cancer Agents

The global burden of cancer is increasing. The expanding use of OAAs is posing major concerns on safety of personal, patients and their caregivers. The standards and guidelines for safe handling and dispensing of these agents a not abreast with the rapid and wide applications of these medications in clinical practice. After collaborative initiatives more comprehensive guidelines addressing safe handling and dispensing of OAAs have been developed, however their uniform implementations remains a major challenge. More studies are needed to identify the areas for improvement relevant to each practice. Pharmacists will remain a key player in safe handling and dispensing these medications as well as educating patients and caregivers. The published studies highlight major gaps in OAAs and safe dispensing. Medical schools, policy makers, institutions, researchers and patient advocates need to work together to improve pharmacists' knowledge and competency as well as the safety of pharmacists, patients and caregivers handling the OAAs.

6. Conclusion and Future Prospects

Early detection, accurate staging and complete surgical removal are crucial in order to successfully treat and potentially cure patients with solid cancers. Molecular imaging techniques have the potential to play an important role in improving cancer diagnosis and treatment by expanding existing whole body imaging modalities to a functional, cellular level as well as enhancing intraoperative visualization of diseased and healthy tissues for surgeons. PET imaging has already established itself as an indispensable and truly molecular imaging modality in today's clinical routine. However, currently developed molecular imaging probes for US and especially MRI may soon allow for a more specific detection and accurate visual enhancement of cancer cells while at the same time providing information about their invasiveness and bimolecular production profiles.

Drawing a clear conclusion is difficult because of the low level of evidence/study design and low methodological study quality. However, it seems that adherence enhancing interventions could have an effect, if the baseline adherence is considered when choosing eligible patients to

avoid ceiling effects. Especially educational and counselling interventions seem promising. A reason could probably be that educational and counselling interventions mostly target several of the adherence influencing dimensions.

Although the newer generations of anticancer agents which can be delivered orally are at priority in developmental pipeline, the classical drug substances can also be delivered efficiently via specific formulation design approach. The poor physicochemical and biopharmaceutical properties associated with the various anticancer drugs hindering their oral deliverability can be effectively circumvented by utilization of absorption enhancers (P-gp inhibitors and functional excipients) and pharmaceutical approaches such as nanocrystals and nanocarriers. These novel drug delivery systems owing to their special properties are able to bypass various barriers of drug delivery across the gastrointestinal tract. Furthermore, the targeting potential of these systems is of special interest in the cancer therapy. Passive targeting via enhanced permeation and retention is one of the common and important advantages offered by almost all types of nanocarriers. The oral delivery of anticancer agents via such drug delivery systems is of great interest for improving the quality of life of patients suffering cancer. In addition, the pharmacoeconomic advantage with oral delivery of 'injection only' drugs will fetch significant attraction of health care agencies by reducing the overall cost incurred in health care management.

In an attempt to design a new material for local drug delivery systems, a conjugated polymer/triterpenoid composite has been described and demonstrated to be a robust and cost-effective system. An initial, one-step fabrication procedure provided layers exhibiting good drug release properties, with the drug retaining its anticancer activity. Investigation of obtained systems and implementation of modifications revealed another route of fabrication.

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Citation: *Dr. Jyoti Chopra. The Other Side of Oral Anti-Cancer Agents: Boon or Disguise. ARC Journal of Dental science. 2018; 3(3):11-17. doi:dx.doi.org/ 10.20431/2456-0030. 0303004.*