Anita ŠIMIĆ

UNIVERSITY HOSPITAL CENTRE ZAGREB, KIŠPATIĆEVA 12, ZAGREB, CROATIA
anita.simic@kbc-zagreb

Implementation of new information technologies in the central preparation of antineoplastic drugs

Key words: central preparation of antineoplastic drugs, application system,gravimetric method, quality assurance

One of the central places of health care institution is the centralantineoplastic preparation unit under the jurisdiction of a pharmacy. Under controlled conditions, in accordance with the prescribed measures for the protection of staff and preparations, "ready to administer" parenteral preparations of antineoplastic drugs are prepared for oncological and other indications.

Narrow therapeutic index of cytotoxic drugs requires precise dosage in order to ensure optimal concentration that will result in the desired pharmacological effect. An overdose of cytotoxic drugs can be a cause of toxic and undesirable effects. Using sub-therapeutic doses would not provide sufficient concentration to manifest wanted therapeutic effect.

Traditionally, the preparation of cytotoxic drugs is a volumetric method of preparation whereby a certain volume of a diluted or reconstituted drug is prepared in an infusion solution. In this case, the accuracy control of a given volume is performed visually.

By using the gravimetric method of preparation of the cytotoxic drugs that are being administered intravenously, using the new information technology solutions, the dose of the drug to be prepared is quantitatively determined. At each step of the preparation, the mass of the particular solution is measured by electronic scales.this also increases the safety and quality of the prepared therapies.with automated data entry, drug monitoring capability, documenting all processes, and savings during preparation, additional value is created.

An additional challenge is the proper integration with hospital information systems. The challenges we face in the implementation phase emphasize existing problems and can even make them worse. By properly integrating new technologies into an already successful workflow we can improve security, establish enhanced workflow control, monitoring capacity and more efficient resource distribution.

Marko SKELIN

GENERAL HOSPITAL ŠIBENIK, PHARMACY DEPARTMENT, STJEPANA RADIĆA 83, ŠIBENIK, CROATIA
marko.skelin@bolnica-sibenik.hr

Concurrent cisplatin-based chemoradiotherapy *versus* cetuximab-based bioradiotherapy for p16-positive, locally advanced oropharyngeal cancer: a meta-analysis

Key words: oropharyngeal cancer, human papilloma virus, cisplatin, cetuximab, survival, recurrence

A special entity among head and neck squamous cell carcinoma is represented by human papilloma virus (hpv) associated oropharyngeal cancer (opc). Given its favourable prognosis, one of the de-escalating strategies in the treatment of opc includes the replacement of cisplatin (cddp) with cetuximab (c225). The aim of this study was to perform a meta-analysis of published studies which directly compared the efficacy of cddp *vs.* C225 given concurrently with radiotherapy (rt) as definitive treatment of p16-positive opc. A systematic literature search was performed for studies published between 2006 and 2018. A total of 1417 citations were obtained and six studies met inclusion criteria, with a

total of 526 patients. The data from 5 studies were available for the analysis of 2-year overall survival. The pooled odds ratio (or), calculated for cddp + rt *vs.* C225 + rt, was 0.35 (*p=0.003*). The data from 6 studies were available for the analysis of 2-year locoregional recurrence. The pooled or, calculated for cddp + rt vs. C225 + rt, was 0.25 (*p<0.0001*). Patients receiving cddp with irradiation had 2.9 and 4-fold decreased risk for death from any cause and locoregional recurrence, respectively. Cddp-based chemoradiotherapy should remain standard of definitive treatment of p16-positive opc.

Olivera SPASOVSKA

UNIVERSITY CLINIC OF ABDOMINAL SURGERY, MOTHER THERESA 17, SKOPJE, R NORTH MACEDONIA

Clinical pharmacist as a part of multidisciplinary team in treatment of oncology patient

When we look at the multidisciplinary team working with cancer patients, we focus on the front line health care professionals-oncologist, pathologists, radiologists, nurses and other vital to providing the best care. But there is another major group of proffesionals that has had to fight hard for recognition of their contribution. Pharmacsit play a key role in the health care team through the provison of high quality medication, appropriate information on treatmen schedules and effects of medication, as well as advice on the management of adverse events and use of complementary treatment.

Degree of implementation of clinical pharmacy practise in the health care system is different .the highest is in higly developed countries such as canada, usa, uk.. In europe, althought there was some progress, it can not say that pharmaceutical services are fully implemented.

In macedonia, there is lack of clinical pharmacist, national guidelines and standard operative procedures for the responsinilities of clinical pharmacist.

It is very important for clinical pharmacist to know, who are the expectations of health wokers from them and why do they need pharmacist.

Although pharmacist contributions to oncology have not been fully recognised, there is reason to be optimistic that clinical pharmacist will have an expended role on oncology teams.

Introducing individualised treatment plans, monitoring chemotherapy together with nursing staff, and providing patient education about medications could serve as starting points for introducing clinical pharmacist to multidisciplinary oncology teams.

Multiproffesional teams are key to a good outcome. As clinical pharmacist have the precise knowledge about antineoplastic drugs and regular interaction with prescribers, they are ideally placed to bridge the gap between patients and oncoligy phisicians. Both pharmacist and oncology physicians are learning to form multiprofessional teams.

Marija PETKOSKI[1], Mirjana ANTUNOVIĆ[1], Vesna PUTIĆ[1], Mirjana BOŠKOVIĆ[1], Dragana MILOVANOVIĆ[1].

[1] MILITARY MEDICAL ACADEMY, CRNOTRAVSKA 17, BELGRADE, SERBIA

Stability of the infusion preparation after centralized preparation drugs

Key words: stability, doxorubicin

Introduction: The preparation of cytotoxic drugs involves reconstitution of commercial drugs. Reconstitution is usually carried out in the departments of clinics in uncontrolled conditions. The disadvantages of such an organization disturb sterility and quality of applied medicine, inadequate health care and violation of the medical staff, the lack of documentation on the preparation and control of the drug and the possibility of irrational consumption of drugs.

By centralized drug reconstitution, the sterile preparations are stable for more than 24 hours.

Physical chemical preparations can be stable for longer than 28 days.

Under the hospital pharmacy conditions, studies of the practical stability of Doxorubicin solution, concentration of 0,04mg/ml, were carried out.

Materials: Doxorubicin Ebewe®, solution for injection/infusion, 50mg/25ml. Sodium chloride 0.9%, 500 ml. Acetonitrile, sodium dihydrogen phosphate, phosphoric acid, methanol, purified water were HPLC reagents with appropriate purity grade.

Methods The preparation was stored at a temperature of 2-8 degrees. Clearance testing and potentiometric determination of pH were used as physical stability tests, according to Ph. Eur. 9.0. For chemical testing, Doxorubicin content was determined by HPLC method.

Results and discussion:

Repeatet of the solution at room temperature did not cause degradatio. No physical instability of Doxorubicin solution was detected during observation period. The prepared Doxorubicin solution remained clear. By potentiometric pH determination, the test Doxorubicin solution had pH = 5.35-5.40, which corresponds to the pH value interval in which the drug is the most stable (USP35/NF30).

The preparation was examined during time intervals (1st-7th, , 10th 14th and 28th day).

The concentration of doxorubicin over a time interval was within the limits of 97.1%-99.99%

which corresponds to the limits where we can confirm the chemical stability of doxorubicin.

Conclusion: By analyzing the obtained results we can say that the preparation doxorubicin 0,04mg/ml is stable for 28 days

Dragana MILOVANOVIĆ[1*], Mirjana ANTUNOVIĆ[1], Vesna PUTIĆ[1], Mirjana BOŠKOVIĆ[1], Marija PETKOSKI[1].

[1] MILITARY MEDICAL ACADEMY, CRNOTRAVSKA 17, BELGRADE, SERBIA

dramilovanovic@gmail.com

Practical stability study under the hospital pharmacyconditions

Key words: stability, 5-fluorouracil

Introduction: Cytotoxic drugs are known to be very toxic to the cells, primarily for those in the phase of division. In order to achieve the desired therapeutic effect with minimal side effects, it is necessary to provide the appropriate quality of the drug. In addition to industrial production, cytotoxic drugs often require reconstitution/dilution under the pharmacy conditions. As the stability of the cytotoxic drug, manufacturers specify a period of 24 hours after opening, seen only from the aspect of microbiological stability. Given that the manufacturer's recommendations do not consider the chemical stability of medicines, and the preparation and administration of medicinal products is carried out under aseptic conditions, the shelf-life of the preparation may be extended. Under the hospital pharmacy conditions, studies of the practical stability of 5-fluorouracil (5-FU) solution, concentration of 1.5 mg/ml, were carried out.

Materials: 5-Fluorouracil Ebewe®, solution for injection/infusion, 5000mg/100ml. Sodium chloride 0.9%, 500 ml. Acetonitrile, sodium dihydrogen phosphate, phosphoric acid, methanol, purified water were HPLC reagents with appropriate purity grade. Substrates: Columbia agar®, Mac Conkey agar®, Sabouraud dextrose agar® were used for microbiological stability tests of 5-FU solution.

Methods: Clearance testing and potentiometric determination of pH were used as physical stability tests, according to Ph. Eur. 9.0. For chemical testing, 5-FU content was determined by HPLC method. Method of microbiological testing was incubation of 5-FU solution into the substrates.

Results and discussion: No physical instability of 5-FU solution was detected during observation period. The prepared 5-FU solution remained clear. By potentiometric pH determination, the test 5-FU solution had pH = 9.01 - 9.07, which corresponds to the pH value interval in which the drug is the most stable (USP35/NF30). 5-FU content was determined at appropriate time intervals (1st-5th, 7th, 10th and 28th day). The content of 5-FU in solution over time was 96.60% - 99.93%, indicating that the degradation of the active substance is small, and the solution can be considered chemically stable. The microbiological stability test was performed by seeding on the substrates on the 28th day of the test, to determine if the sterility of the preparation was preserved. After incubation at a temperature of 37°C for 24 to 48 hours, the substrates remained sterile. This confirmed the microbiological stability of the preparation.

Conclusion: Based on the results obtained, it can be concluded that the prepared 5-FU solution remained stable for 28 days.

Eugen JAVOR

GENERAL HOSPITAL BJELOVAR, MIHANOVIĆEVA 8, BJELOVAR, CROATIA

eugen.javor@gmail.com

Oncolytic viruses in cancer therapy

Key words: oncolytic viruses, T-VEC, immunotherapy

For more than a century, viruses are the subject of interest in cancer therapy, but in the last few years, patients might finally have benefit from this approach. Oncolytic viruses are viruses that aim to enter the cancer cell, selectively replicate there and ultimately kill the cancer cell. Immune response to oncolytic viruses becomes an important component of antitumor activity. Oncolytic viruses warn the immune system that something is wrong. This can lead to an immune response against nearby tumor cells (local response) or tumor cells in other parts of the body (systemic response).

Immunotherapy with oncology viruses is currently undergoing a renaissance, and several types of oncological viruses have progressed to the last stages of clinical research [1]. For now, the only oncolytic virus approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) is Talimogene laherparepvec (T-VEC) in the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease[2,3]. T-VEC is a weakened Herpes simplex virus 1 (HSV-1) derived by functional deletion of 2 genes (ICP34.5 and ICP47) and by insertion of the coding sequence for human granulocyte and macrophage colony stimulating factor (GM-CSF). T-VEC is tested in clinical trials and as a supplement to immunotherapy [4].

One is certain. The field of therapy with oncolytic viruses is rapidly developing and will certainly contribute to the progress in the treatment of certain cancers in the years ahead.

REFERENCES:

1. Clinical Program. VYRIAD. Available at: http://www.vyriad.com/pipeline/ Accessed: 11 March, 2019.
2. EPAR product information. Available at: https://www.ema.europa.eu/en/documents/product-information/imlygic-epar-product-information_en.pdf. Accessed: 11 March, 2019.
3. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. Available at: https://www.fda.gov/downloads/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm469575.pdf. Accessed: 11 March, 2019.
4. Ribas A, Dummer R, Puzanov I, et al. Oncolytic virotherapy promotes intramoral T cell infiltration and improved anti-PD-1 immunotherapy. Cell. 2017. doi: http://dx.doi.org/10.1016/j.cell.2017.08.027

Katarina VUČIĆEVIĆ

DEPARTMENT OF PHARMACOKINETICS AND CLINICAL PHARMACY, FACULTY OF PHARMACY – UNIVERSITYOFBELGRADE, VOJVODE STEPE 450, 11221 BELGRADE, REPUBLIC OF SERBIA

The importance of pembrolizumab and nivolumab pharmacokinetics in the treatment of oncology patients

Key words: disposition, variability, PK-PDrelationship, monoclonal antibody.

The use of monoclonal antibodies (mAt) in the treatment of oncology patientshas expanded significantly in the last 5 years, as clinical studies and practice have confirmed better treatment outcomes and longer survival with less toxicity,at the same time. All currently registered drugs have the same basic structure, which corresponds to immunoglobulin G (IgG). mAt acting as inhibitors of immune checkpoint inhibitors (ICI), such as pembrolizumab and nivolumab, significantly improved the prognosis of patients with melanoma, non-small cell lung carcinoma, classical Hodgkin's lymphoma and other malignancies. Pembrolizumab is a potent, highly selective, IgG4-kappa humanized mAt, while nivolumab is a human IgG4. Both drugs prevent the interaction of programmed cell death (PD-1) and its ligands (PD-L1 and PD-L2). Understanding the pharmacokinetic profile of the drug as well as its association with the efficacy and safety profileis necessary.

High interindividual pharmacokinetic variability of mAt ICI (>30%) was observed in the clinical studies, and it is only partially described using demographic and individual clinical characteristics of patients. Both drugs are administeredvia a 30-minute intravenous infusion,hence their bioavailability is complete. Dosing regimen of these drugs is largely dependent on the tumor type. Therefore, doses of pembrolizumabare 2 mg/kg or 200 mg every 3 weeks, whilenivolumabis administered at doses of 3 mg/kg, 240 mg or 480 mg every 2-4 weeks. The pharmacokinetic behavior of mAtconsiderably differs from the chemical drugs.In general,mAt have a low volume distribution due to limited distribution in the extracellular area (volumen of the central compartment is about 3.5 L, while the peripheral 3-4 L), a long half-life (approximately 25-27 days), and the target receptor-mediated disposition with dose and/or time-dependent and independent clearance. The average clearance of pembrolizumab is 0.168-0.249 L/day, whilenivolumab'sis about 0.36 L/day. Significant interindividual(about 35%) and interoccasionalvariability during the treatment(25%) in the clearance has been identifiedfor these drugs. They are primarily metabolized by degradation to smaller peptides and amino acids in many tissues of the organism,similarly as endogenous Ig. In order to establish exposure-efficacy relationship, so far,different parameters have shown a satisfactory correlation. Thus, minimum, average concentrations in the steady-state and clearance are correlated with one of the following parameters: response to therapy (partial or complete), overall survival, reduction of tumor size.

Since pembrolizumab and nivolumab are relatively novel drugs, there is still insufficient data and evidences on the possibilities to individualize therapy, taking into account the individual pharmacokinetic profile of the drugs. Therefore, the purpose of this lecture is to provide insight into pharmacokinetics and pharmacokinetic variability of pembrolizumab and nivolumab, and the relationship with the efficacy of the drugs.

Monika SONC

INSTITUTE OF ONCOLOGY LJUBLJANA, SLOVENIA

Pharmacovigilance: Monitoring of the Adverse Drug Reactions

At the Institute of Oncology Ljubljana monitoring, recording and reporting ofadverse drug reactionsis particularly importantbecausea lotof new drugs are used in cancer treatment. Evenafter thedrugreceivesmarketing authorizationand can be usedin

hospitalsordoctorsmay prescribe it, we have tomonitorthe safety ofmedicines. These activities, which are relatedto the detection,assessment, understandingandprevention of adverse effects, are known aspharmacovigilance. Bycollectingand analyzing the informationon adverse drug reactionswe may help tocomplement theleaflets and thereby improve thesafety of the treatment. It is particularly importantto recordandcollectreports of seriousadverse drug reactions, which is obligatory for all healthcare professionals.

Hospitalpharmacists, whooperateunderthe auspices of the Slovene Chamber of Pharmacy, took theinitiative to prepare theweb applicationwhich facilitates thecollection of data onadverse drug reactions and provides comparable data. We are monitoringespecially adverse drug reactions of anticancerdrugs, which are used to treat the patients in our hospital. The therapy of cancer patients requires continuouslysupervision of the progress of treatment by the physician and pharmacist, since patient oftengets his oral medication atthe community pharmacy.

KRNIĆ, Darko

CROATIAN AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES (HALMED)

Challenges of safe use of oncological drugs

The task of the Agency for Medicinal Products and Medical Products (HALMED) is to promote safe use of medicines, which is of particular importance in the field of the use of oncological drugs. In the lecture will be presented a system of reporting suspected adverse reactions in Croatia, reviewing suspicions about side effects for oncological drugs and trends in reporting suspected side effects of this drug group over the last few years.

Information on suspicions of adverse drug reactions from oncological drugs was obtained from the national, European and world base side effects by filtering reports according to ATK classification. Descriptive data analysis was performed, with special emphasis on the indications of the drugs used, the characteristics of the reporters and the severity of the reaction reported.

The analysis of suspected adverse reaction reports confirms the known safety profile of oncological drugs. The most frequent reports of suspected adverse reactions were sent by healthcare workers, which ensures their quality in detection of safety signals.

Reports of adverse reactions are a valuable source of information on drug safety. Strong partnership between regulatory institutions and health workers is needed to systematically address the issue of awarenessabout the safe use of medicines.

REFERENCES:

1. Medicines Act (Official Gazette 76/13 and No. 90/14).
2. Ordinance of Pharmacovigilance (Official Gazette, No. 83/13.)
3. Guideline on Good Pharmacovigilance Practices (GVP) Module VI - Management and reporting of adverse reactions to medicinal products, Rev.1 (08. 09. 2014.)

Vesna PAVLICA

DEPARTMENT OF HOSPITAL PHARMACY, UNIVERSITY HOSPITAL FOR TUMORS, SESTREMILOSRDNICE UNIVERSITY HOSPITAL CENTER, ZAGREB, CROATIA

Education in oncology pharmacy

Oncology Pharmacy is a specialized branch of pharmacy which includes a pharmacist's activity and service, which complete the personalized treatment of the patient. That presupposes a rational and optimized use of drugs, and activities complementary to those of other medical professionals.

A pharmacist will take part in the work of a multiprofessional health care team focusing on oncology pharmacy and oncology pharmacy practice. Oncology pharmacy practice includes activities such as: handling antineoplastic drugs and counselling oncology patients.

In order for an oncology pharmacist to take part in professional counselling in everyday work, a special education and training are required. That is why the graduate course at the Centre for Applied Pharmacy performs education and professional training

as a part of the subject entitled: Pharmaceutical Care. Students acquire knowledge relative to pharmaceutical care for an oncology patient. A total of 13 periods of education in Oncology Pharmacy take place as a part of a Specialized Course in Clinical Pharmacy. As a part of subject Pharmacotherapy in Clinical Oncology, specializing interns spend a month in the Medical Oncology Ward of the University Hospital for Tumors of the Sestre milosrdnice University Hospital Center. Practical work in Oncology Pharmacy takes place in the pharmacy of the same clinic, for two months.

Likewise, a subject of Pharmacotherapy of Malignant Diseases (15 periods) has been introduced at the fifth year of the Pharmacy Course of the Pharmaceutical - Biochemical Faculty of the Unversity of Zagreb.

The Centre for Applied Pharmacy of the Pharmaceutical Biochemical Faculty of the University of Zagreb organizes the student internship and Professional Training for Pharmacists, a total of 720 hours. The programme is based on the Croatian Pharmaceutical Competency Framework and contains a list of activities to be undertaken for achieving the expected competencies for student interns. There is a special programme within it for the students who want to spend this part at the University Hospital for Tumors. These are the issues a special emphasis is placed on: safe handling of antineoplastic drugs, optimization of therapy by providing pharmacists' care to the oncology patient and side effects.

Everyday work at the University Hospital for Tumours takes place at the Medical Oncology Ward, at the outpatients clinic, day hospital and at the pharmacy. Education also takes place as a part of pharmaceutical counselling of oncology patients concerning the application and coordination of drugs and nutrition supplements. Patient counselling is intended for all oncology patients and their family members who wish to get educated on the over the counter drugs, herbal drugs and nutrition supplements. Such counselling is performed in order to prevent medical errors and drug interaction, to have therapy harmonization, perform patient counselling on therapy adherence and educate on the need for strict control of nutrition supplements.

Vesna PAVLICA

HOSPITAL PHARMACYDEPARTMENT , UNIVERSITY HOSPITAL FOR TUMORS, SESTRE MILOSRDNICE UNIVERSITY HOSPITAL CENTER, ZAGREB, CROATIA

Digital Pharmacy

Health care, at all levels of everyday life, is gaining in importance: in society, at the level of biomedical sciences, technological sciences and at the level of consciousness of healthy and sick individuals. Health care is also constantly evolving. Modern technologies provide more effective ways of treating diseases. Over the past two decades, the Internet has changed the way in which information is accessed. Mobile devices moved this a step further, allowing users remote access to the World Wide Web. Such devices are now more numerous than personal computers and will soon become the most common way of accessing data. Mobile applications can provide healthcare professionals with the opportunity to quickly and easily access important medical information that directly affects the patient's health care, and thus to rational pharmacotherapy, treatment outcomes, transparency in work and significant financial savings. The FDA registered the first digital drug. The PillCam COLON system allows direct colonic visualization when the colonoscopy is not the best option for the patient. A dual camera is placed in the volume of the capsule of the usual size for the drug. Assessing the quality of health applications (there are more than 110 000 on the market) is very difficult, if health professionals do not know which tools to use. Pharmacy, as a complex biomedical science, increasingly integrates with medicine and information technology into a specific ecosystem that significantly contributes to improving health care, preventing disease and improving the quality of life and patient safety. It is up to us to open new areas of cooperation, get directly involved and decide on pharmacy's present and future.

Nataša JOVANOVIĆ LJEŠKOVIĆ[1], **Claudia RIJCKEN**[2,3]

[1] FACULTY OF PHARMACY NOVI SAD, UNIVERSITY BUSINESS ACADEMY NOVI SAD, TRGMLADENACA 5, NOVI SAD, SERBIA
[2] PHARMACARE.AI, HIGH TECH CAMPUS 27, EINDHOVEN, THE NETHERLANDS
[3] UTRECHT UNIVERSITY, UTRECHT, THE NETHERLANDS

Digital transformation of pharmaceutical care: the challenges and the opportunities

We are living in the era of 4th industrial revolution followed with accelerated technological development, robotization and digitalization of all sectors. Medicine and pharmacy are also going through digital transformation and significant changes are yet to come.

Smart phones, sensors and other tracking devices are already around us; technologies based on artificial intelligence (AI) are blooming so it can be foreseen that in (relatively near) futureit would be possible to get a diagnosis for some common medical conditions via smart phones. It is feasible to visualize the patients monitored on a distance by highly sophisticated health devices and assisted by various virtual voice-assistants and/or humanized robots.Via some application it will be possible to receivediagnosis followed by a prescription and in the pharmacy personalized medicine will be printed in the 3D printer. And this is not a science fiction but a part of very predictive future based on the AI, big data, internet of things and many other powerful technologies.

It is expected that the digitalization will speed up many of the important processes and help to overcome some of the major challenges that the health system of modern age is facing: ageing population, rising medical costs, medical waste, early- and predictable diagnostic, treatment of life threatening and chronical diseases. However, intensive development of new technologies and fast digitalization rise some questions and doubts among the pharmacists and health professionals in general: Are we ready for digital transformation? Are the pharmacists/health professionals still needed in the future or are they going to be replaced by robots/AI?

The aim of this work is to present that the technology and digital health tools should not replace but enhance and support the role of pharmacists in pharmaceutical care, enabling more quality time for the patients and for the core role of the pharmacistas highly-educated professional who is responsible for assuring optimal impact of the therapy.

It is obvious that transit through digital transformation will require changes: starting from the education, setting lifelong learning programs, acquiringdeeper insights in new technologies, changes in defining of daily responsibilities of pharmacists. However, digital transformation is an opportunity and now is the time for the pharmacists to get involved, to take a proactive role in the fast-changing world and to explore how and which digital health tools can enhance their profession and position of the medication experts.

Andreja EBERL[1]

[1] ONKOLOŠKI INŠTITUT LJUBLJANA / INSTITUTE OF ONCOLOGY LJUBLJANA
aeberl@onko-i.si

The role of pharmacists in management of oral anticancer drug therapy

Key words: **P**harmaceutical Services, oral anticancer drugs, counselling

Oncology is undoubtedly currently the fastest developing area of healthcare. More or less every month new drugs come to the market; many of them are formulations for oral administration. Anticancer therapies are increasingly shifting from clinic-based infusions to orally- administered medications by patients and/or their informal caregivers, thereby changing patients and health professionals roles, responsibilities and priorities. This means that the complex treatment of often co-morbid cancer patients is moving from a supervised hospital setting to the patient's

home and dispensing of potent oral anticancer drugs to general community pharmacies. With the narrow therapeutic index of orally available anticancer drugs (OAD), patients are vulnerable to treatment failure and side effects due to medication errors, drug interactions and non-adherence. Thus, these patients need concerted counselling by both the oncologist and the community pharmacist. Effective counselling is vital to ensure patients are able to use their oral chemotherapy in a safe and effective way;therefore,pharmacists'role is crucial, since they are dispensing oral anticancer drugs.

In Slovenia OADs are dispensed by community pharmacists. Within the EPIC project ("Empowering pharmacists to improve health care for oral chemotherapy patients: Establishment of a European best-practice model") we have implemented training programme and an online helping tool which assist pharmacists at dispensing in Slovenia.The online tool ensures that pharmacists could provide appropriate pharmaceutical care for cancer patients receiving OADs. Pharmacists reported that their knowledge improved in all areas covered by training programme and that information in database is very useful therefore, we could conclude that both training programme and e-tool considerably improved pharmacists' knowledge about oncology and oral anticancer drugs and they can provide better counselling and pharmaceutical care for cancer patients. However, the proportion of communitypharmacists who regularly counsel patients about OADs is still too low in view of the importance of the patients' adherence to their therapy.

Dahna ARBANAS

KARLOVAČKA LJEKARNA, KARLOVAC, HRVATSKA
darbanas2611@gmail.com

Pain and a palliative care-a community pharmacy

Key words: pain, palliative care, community pharmacist

Palliative care and hospice programs are specialized pain and symptom management programs. Although the terms often overlap in common usage, palliative care is not synonymous with end- of-life care, and can be provided to patients who are not terminally ill. Palliative care focuses on the prevention and relief of suffering. The term "malignant pain" has historically been used to refer to pain resulting from cancer—either pain caused by tumors themselves or pain caused by treatments such as chemotherapy, radiation, or surgery. However, a newer definition for malignant pain is pain that is "associated with progressive disease that is potentially life limiting". This definition includes pain resulting from conditions such as acquired immunodeficiency syndrome (AIDS), progressive neurological diseases, end-stage organ failure, and dementia. Treatment of pain involves non-pharmacologic and pharmacologic modalities. How can a community pharmacist help to manage pain?

Ljiljana ĐEKIĆ

UNIVERSITY OF BELGRADE – FACULTY OF PHARMACY, DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY AND COSMETOLOGY, VOJVODE STEPE 450, 11221 BELGRADE, SERBIA

ljiljanadjek@gmail.com

Colloidal carriers (nanocarriers) based oncology drugs - characteristics and clinical significance

Key words: oncology drugs; nanocarriers; nanoparticles; liposomes; PEGylation; passive drug targeting.

The available conventional anticancer chemotherapeutics have a number of unique problems including poor aqueous solubility, very short half-life, and development of cancer drug resistance, making the chemotherapy ineffective, while serious side effects often impose reduction, treatment delay, or discontinuance of therapy. Since the mid-1990s, started commercialization and clinical use of oncology nanofarmaceutics i.e., oncology drugs based on the active substance encapsulated in a carrier of less than 1000 nm (nanoparticles). Although a number of nanocarriers have been developed, only a few of them, including liposomes and nanoparticles, are used in oncology drugs approved for the treatment of various tumors. The first liposomal product to obtain regulatory approval for the treatment of ovarian cancer and AIDS-related Kaposi's sarcoma was liposomal doxorubicin (Caelyx®/Doxil®) in 1995, was also the first US Food and Drug Administration (FDA) approved nanopharmaceutic. Such oncology drugs hold a great potential for enhancement of the therapeutic efficacy and safety profile. Nanoencapsulation of anticancer drugs is a suitable strategy for improving solubility, stability and biodistribution of the entrapped drug, depending on the physicochemical features of the nanocarrier. The physicochemical characteristics of nanocarriers can be tuned by altering their compositions, sizes, shapes and surface properties (surface charge, functional groups, coating with polyethylene glycol (PEG), attachment of targeting moieties). When formulating nanopharmaceutics, different strategies can be applied to improve drug efficacy, including: 1) covalent conjugation and active encapsulation approach to increase drug loading, stability and sustained release; 2) exploiting the small size of nanocarriers to circumvent important physiological barriers (the immune system, renal clearance, enzymatic degradation, and others); 3) covalent attachment of PEG, a water soluble and biocompatible polymer, to a drug molecule or nanocarrier (PEGylation), in order to increase the serum half-life (by increasing hydrophilicity and reducing immunogenicity of the nanocarrier and avoiding of reticuloendothelial system (RES)), and by reducing the rate of renal excretion. Such strategies may provide prolonged systemic circulation of a nanoencapsulated drug allowing accumulation within the pathophysiological mileau of tumor tissues due to leaky vasculature and poor lymphatic drainage. The phenomenon is called the enhanced permeability and retention (EPR) effect and is the basis for passive targeting which involves nonspecific accumulation of nanoencapsulated drugs to tumor cells. Targeted cancer therapies are expected to be more effective compared to available conventional treatment procedures. The targeted delivery may cause increased bioavailability and allow dose reduction, minimizing side effects. Significant improvements are already demonstrated in clinical trials and representative examples are oncology nanopharmaceuticals of paclitaxel, PEG-L-asparaginase, doxorubicin, daunorubicin, mifamurtide, and irinotecan. The conducted studies indicate significant differences in biopharmaceutical and pharmacokinetic profiles of nano- and conventional drugs. Most of the nanocarrier based oncology drugs approved to date have demonstrated reduced toxicity rather than improved efficacy compared to conventional formulations. Development of more effective nanocarriers for precise cancer treatment avoiding life-threatening side effects with a positive cost-benefit aspect is a permanentanet challenge.

Robert ŠEPAROVIĆ

CLINICAL HOSPITAL CENTER SESTRE MILOSRDNICE;
UNIVERSITY HOSPITAL FOR TUMORS; ZAGREB

Which goals do we have in treatment of patients with breast cancer?

Anyone who has malignant breast cancer has only one goal and it is to live. In the case of early breast cancer, curing the disease is indeed the primary goal of the treatment. Diagnostic and therapeutic procedures are preformed to define the exact local stage of the disease and to design therapeutic approach (local or systemic), which will provide the best chances for the cure. This will ensure that the quality of life of patient is preserved in spite of the fact that each diagnostic and therapeutic procedure is linked to potential impairment of quality of life. In the advanced/ metastatic disease today, it is not possible to completely destroy the tumor cells, and the primary goal of the treatment is to preserve the quality of life and, of course, delay the time to progression of the disease and prolong survival by keeping the total volume of the disease under control. Each relaps of the disease has the clear impact on the health and quality of life of the patient, but also brings an additional burden on the health system. Importance of neoadjuvant therapy (combination of chemotherapy and targeted therapy) in the treatment of early HER2 positive breast cancer, prior to surgical removal of tumors in the breast and/or axilla, is increasing. This approach can result in reducing tumor volume which enables less aggressive surgical procedure and provides us the information about tumors sensibility to applied therapy which can be monitored radiologically and clinically by palpation. The ultimate goal is the complete disappearance of the tumor, the so-called complete pathological response, which is later associated with better outcomes in terms of longer time to disease progression and better total survival. Unlike the neoadjuvant approach, in the adjuvant approach (in which systematic treatment is used after the surgical procedure), it is not possible to estimate the effect of the drug on the tumor since the tumor has already been surgically removed. This, in some way, makes it difficult to estimate the therapeutic response and complicates the decision on potential additional treatment for the group of patients in whom a complete pathological response has not been achieved. From the point of view of the patient, significant progress has been made with the subcutaneous formulation of trastuzumab, because the time spent in the hospital is shorter and allows the patient to have more free time during the day. On the other hand, there is a whole range of organizational advantages in daily work of the day hospital that enables greater flow, flexibility and lower costs, and prevents dosing errors.

Ana TEČIĆ VUGER

CLINICAL HOSPITAL CENTER SESTRE MILOSRDNICE;
UNIVERSITY HOSPITAL FOR TUMORS; ZAGREB

What are the main characteristics of HER2 positive breast cancer?

HER2 positive cancer is a subgroup of breast cancer with aggressive biology and it occurs in 15-20% of all breast cancer patients. The increased risk of disease relaps is present even in small tumors, smaller than 1-2 cm. Discovery of targeted therapies (trastuzumab) directed to the HER2 protein, reduced the risk of relaps by 50% in patients with operated local or locoregional breast cancer (tumor in breast and/or axilla). However, every fourth affected person will still have the risk of a disease relaps. In that case, the disease becomes incurable and than one of our goals of treatment is to convert metastatic breast cancer into chronic illness. This is why multidisciplinarity is needed. It provides the best therapeutic approach for each individual patient. The use of neoadjuvant therapy (systemic therapy prior to surgery) has enabled the best therapeutic responses in group of patients with aggressive biology which includes patients with HER2 positive disease. Neoadjuvant treatment consists of chemotherapy and targeted therapy (usually for six months) directed to the HER2 protein. Today's standard is the dual HER2 blockade with

pertuzumab and trastuzumab which provides the highest rate of complete pathological response. In patients who did not achieve complete pathological response after neoadjuvant treatment, newest clinical trials showed significant benefit with the use of adjuvant trastuzumab emtanzine. This combined approach with targeted therapies ensures better efficacy and the best possible treatment outcomes in this moment.

Today, trastuzumab can also be applied in the subcutaneous formulation and we will present specific benefits from the real clinical practice in our oncology center.

Sanda Vladimir-Knežević

DEPARTMENT OF PHARMACOGNOSY, FACULTY OF PHARMACY, UNIVERSITY OF ZAGREB
TRG MARKA MARULIĆA 20, 10000 ZAGREB, CROATIA
svladimir@pharma.hr

Medical cannabis in oncology pharmacy

Keywords: Cannabis sativa, phytocannabinoids, cancer, oncology pharmacy

Cannabis sativa L. (Cannabaceae) is one of the first plants cultivated by man and one of the oldest plant sources of fibre, food and remedies. It has a long history of medical use in the Middle East and Asia, dating back to the sixth century BC. During a period of colonial expansion in the early 19th century cannabis found a way to Western Europe as a medicine to alleviate a variety of conditions, such as pain, spasms, dysentery, depression, sleep disturbance and loss of appetite. In the beginning of the 20th century, due to the availability of substitute drugs, absence of quality control and the risk of abuse and intoxication, cannabis medication fell into disuse. The unfertilised flower heads and flower bracts of the female plant are the primary source of phytocannabinoids as a unique group of terpenophenolic compounds. Since 1970s, phytocannabinoids have been known for their effects on some cancer-associated symptoms such as nausea and vomiting reduction, appetite stimulation and pain relief. The principal active constituent is delta-9-tetrahydrocannabinol (THC), which binds to endocannabinoid receptors to exert its pharmacological activity, including psychoactive effect. The other important molecule of current interest is non-psychotropic cannabidiol (CBD). The therapeutic properties of cannabis have been much debated from scientific and regulatory points of view over the years. The medical use of cannabis is still controversial and strongly limited by unavoidable psychotropic effects. Many countries legalized cannabis for medical purposes, but the use of either plant-derived preparation or pure cannabinoids is still very limited. So far, only three cannabis-based medicines can be prescribed for certain indications. In the context of cancer, dronabinol (synthetically generated THC) and nabilone (a synthetic THC analogue), can be prescribed to prevent chemotherapy-induced nausea and vomiting. Nabiximols, plant extract enriched in THC and CBD at an approximate 1:1 ratio, is approved for the treatment of cancer-associated pain. The medical use of cannabis refers exclusively to symptomatic treatment as an add-on therapy consisted of the individual dose titration phase and the maintenance phase. In addition to the expected therapeutic effect of cannabis, it is important to consider the adverse effects that may occur.