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## Stages of formation and main achievements of the Chemotherapy Department of Kazakh Institute of Oncology and Radiology

*The article talks about the Chemotherapy Department of the Kazakh Research Institute of Oncology and Radiology (KazIOR), which is an important part of cancer patients' treatment in the Republic of Kazakhstan. The roll-out of clinical chemotherapy as one of the main cancer treatment methods was initiated by Professor S.N. Nugmanov, the director of KazIOR, in 1963, three years after the Institute was established. In addition to clinical activities, the department staff conducts research, participates in clinical trials, provides consulting and methodological assistance in consolidating the national chemotherapy service, and develops national clinical cancer treatment guidelines.*

**Keywords:** Establishment of the Chemotherapy Department, clinical protocols, targeted drugs.

The history of the establishment of the Kazakh Institute of Oncology and Radiology (KazIOR) under the Ministry of Healthcare of the Republic of Kazakhstan (RK) goes back to the era of the intensive development of domestic medical science in the postwar years. The roll-out of clinical chemotherapy as one of the main cancer treatment methods was initiated by Professor S.N. Nugmanov, the director of KazIOR, in 1963, three years after KazIOR was established. N.I. Dementieva, Candidate of Medical Sciences, the first head of the Chemotherapy Department (Figure 1), has gathered talented doctors such as A.I. Tsoi, V.A. Fedina, S.K. Kusherbaeva, F.M. Omarova. Later, they became prominent scientists and organizers of chemotherapeutic service in the RK.



Figure 1 –Candidate of Medical Sciences N.I. Dementieva, the founder of the Chemotherapy Department (1963)

Over the years, the Chemotherapy Department was headed by the Candidate of Medical Sciences A.I. Tsoi,

prof. B.V. Monakhov, prof. N.A. Chichua, the Doctor of Medical Sciences S.E. Yessentayeva, the Candidates of Medical Sciences A.O. Turesheva, K.K. Smagulova, R.Z. Abdрахmanov. Each of them contributed to the development of the science and practice of clinical oncology.

From the first days, the priority directions of chemotherapy at KazIOR included the development and improvement of treatment methods for the most common malignant neoplasms in the RK – esophageal, stomach, lung, breast, colorectal cancers. Due to an asymptomatic course of the mentioned cancers, the patients were mainly admitted with locally advanced processes that limited operating treatment capacity [1].

In the 1960s and 70s, esophageal, stomach, and lung cancers were mainly treated with separate first-generation cytostatics, which delivered only palliative effects of no clinical significance. Further improvement of treatment has shown the promise of a combination of anticancer drugs alone or together with radiation therapy [2].

In the 1980s, the main focus was on the development of an induction chemotherapy regimen as the first stage in the combined treatment of tumors. This approach appeared to be especially efficient in advanced esophageal cancer, with the limited possibility of surgery. Chemotherapy followed by radiation therapy delivered a 1.5-2 times better antitumor effect than radiation therapy alone.

In the 1990s, long-term intravenous infusion chemotherapy (LIIC) was introduced at the Chemotherapy Department to treat esophageal and stomach cancer.

This technique met all the expectations of Kazakhstani scientists since it increased the number of patients with complete and significant tumor regression and, as a final result, significantly improved the survival rates in comparison with routine treatment methods. The

same years witnessed the development of the intermittent mode of cytostatic administration during LIIC. This method enhanced the antitumor effect of cytostatics and was particularly efficient against advanced gastric cancer.



Figure 2 – A meeting of the Chemotherapy Department; in the center – Candidate of Medical Sciences A.I. Tsoy, head of the Chemotherapy Department (1980)



Figure 3 – Senior researcher, Candidate of Medical Sciences B.V. Monakhov, taking cellular material from the esophagus using a self-designed exfoliative probe (1973).

Experimental studies of the KazIOR Radiobiological Laboratory, carried out by Doctor of Medical Sciences, Professor M.L. Efimov, Doctor of Biological Sciences, Professor G.S. Vasilieva, and then a candidate of biological sciences T.G. Goncharova, showed the dependence of the effectiveness and safety of anti-

cancer drugs on the time of administration of drugs during the day and formed the basis of scientific studies to assess the effectiveness of the chronotherapeutic approach in the treatment of disseminated forms of breast cancer. The optimal time of cytostatic administration was determined individually for each patient

based on studying the body acupuncture points' diurnal rhythms. The research results were presented in the thesis of S.E. Yessentayeva (2005).

According to the Department's scientists (N.A. Chichua, S.E. Yessentayeva), the introduction of the metronomic method of anticancer drug administration in treating metastatic breast cancer allowed achieving an objective response in 82% cases on average versus 51% in standard regimens [ 3 ].

The beginning of the XXI century was marked by a new, personalized approach to cancer treatment. The discovery of molecular and genetic mechanisms of carcinogenesis laid the foundation of the so-called targeted therapy. New drugs target growth factor receptors, proteins that carry out mitogenic signals from receptor molecules (non-receptor tyrosine kinases, proteins of the Ras family, cyclin-dependent kinases, etc.), and molecules that control apoptosis and angiogenesis. Clinical oncology receives new effective drugs to treat refractory tumors, such as kidney cancer, liver cancer, non-small cell lung cancer, breast cancer, chronic myeloid leukemia resistant to standard chemotherapy, colorectal cancer, and head and neck tumors.

The research conducted at the Chemotherapy Department of KazIOR investigated the molecular prognostic and predictive markers in clinically unfavorable disseminated breast cancer. These were the first independent studies of the Institute in the field of personalized medicine [4].

The Department has developed and introduced since 2005 a method of regional (intra-arterial) chemotherapy in patients with CRC metastases in the liver. The applied chemotherapy regimens – Oxaliplatin + 5FU / Leucovorin and Irinotecan + 5FU / Leucovorin – led to a subjective improvement and increase in the quality of life in 30% of patients from each group; a therapeutic effect was achieved in 26.7% and 30% of cases; the remission was prolonged by 5.2 and 5.5 months thus increasing the life expectancy up to 15-17 months (A.K. Tumanova, 2009).

Studies on the efficacy of chemotherapy and targeted chemotherapy using modern combinations of cytostatics and targeted drugs in disseminated colorectal cancer showed an objective effect in 45.4% of patients, without pronounced toxic effects. The one- and two-year survival was 84.8 and 77.1%, respectively. The significance of Her 2 / neu overexpression in CRC patients was assessed. Her 2 / neu overexpression found in only 3 (7.1%) out of 42 examined patients correlated with low survival: all those patients died within one year [5].

Currently, the Chemotherapy Department continues the study of the prognostic significance of molec-

ular genetic characteristics in CRC. The detected KRAS mutation frequency in CRC patients in the Republic of Kazakhstan (44.9%) was similar to global values (~40%). G12 D mutation was most frequent in both sexes. G12C and G12S mutations were most rare (less than 5% of patients of both sexes). Thus, such patients require the KRAS gene mutation status definition since it plays an important role in drug treatment strategy determination. The assessment of wild-type KRAS incidence in the RK has shown that 55.1% of CRC patients need targeted therapy with EGFR tyrosine kinase inhibitors [6].

Rapid drug therapy development in the 2000s delivered principal new anticancer drugs. The development of therapeutic regimens based on the latest generation cytostatics changed the possibilities of treatment of tumor diseases. E.g., KazIOR has developed and introduced complex methods of treatment of several diseases in which anticancer drug therapy precedes surgical treatment, such as esophageal and stomach cancer (N.A. Chichua), non-small cell and small cell lung cancer (B.V. Monakhov, A.O. Turesheva), breast cancer (S.E. Yessentayeva), head and neck tumors (B.V. Monkakhov, R.R. Valeev), and CRC (K.K. Smagulova). The new treatment reduces the tumor mass, impacts non-visualizable micrometastases, and lowers the disease stage.



Figure 4 – Doctor of Medical Sciences, Head of Chemotherapy Department N.A. Chichua and Candidate of Medical Sciences A.O. Turesheva (2000)

2001 can be called a new stage in the development of the cancer service of the RK. This year, for the first time since Kazakhstan gained independence, with the support of the state and on the initiative of the Director of KazIOR, professor, academician of the Republican Academy of Sciences of the RK, Doctor of Medical Sciences Zh.A. Arzykulov, as well as the doctors and employees of the Chemotherapy Department, the Mazhilis allocated the state budget KZT 834 million for drug provision of cancer patients. All oncological institutions of the country were provided with a list of anticancer drugs of 37 items, which was one of the effective indicators of the cancer service of that period. Since 2002, oncology was included in the list of socially significant diseases along with such nosologies as diabetes mellitus, tuberculosis, pediatric hematology, and chronic kidney disease. From 2002 to 2006, KazIOR was the coordinator of the drug supply pro-

gram for cancer patients in the Republic of Kazakhstan. Chemotherapist S.E. Yessentayeva was the direct executor of the program.

Understanding the growing importance of drug therapy in treating malignant tumors and the appearance of new target drugs in clinical oncology demanded to change the national structure of oncological dispensaries in RK since the existing structure was mainly oriented on surgical approaches in cancer therapy. The absence of chemotherapy departments, the lack of specialists in drug therapy of tumors set the task for KazIOR and the Chemotherapy Department of KazIOR to train doctors-chemotherapists. A chemotherapy department was then functioning only in Karaganda oncological dispensary, while other dispensaries conducted chemotherapy in surgical departments. Subsequently, 15 chemotherapy departments were organized in various regions of the RK.



Figure 5 – Training of doctors-chemotherapists in the Republic of Kazakhstan (2002)

Since 2003, the Chemotherapy Department of KazIOR was offering regular courses for education and training of chemotherapists. N.A. Chichua, S.E. Yessentayeva, and K.K. Smagulova delivered basic knowledge on drug therapy of malignant tumors to many leading chemotherapists of the country, including R.Z. Abdrakhmanov, D.T. Aryzbzhanov, L.M. Batyrov, R.B. Esengalieva, O.A. Krimmel, A.B. Bolatova, Yu.A. Starchenko, K.R. Umarov, A.D. Urazova, I.V. Voytova, M.A. Akbarova, K.I. Niyazbekova. Later, these doctors headed chemotherapy departments in their dispensaries.

In the same period, doctors and middle managers received an opportunity to participate in internation-

al conferences, congresses, and symposia, study in the world's leading cancer centers, and take part in international clinical trials of promising anticancer drugs in the framework of international cooperation.

The development of chemotherapy influenced changes in the Chemotherapy Department. The bed capacity has grown from 40 to 80 beds; in early 2010, a day patient chemotherapy unit was opened. The Candidate of Medical Sciences Aliya Elbekovna Utelbaeva, the first head of this structural unit, has completed an internship at the day hospital of the National Cancer Institute Regina Elena of Rome.



Figure 6 – Training of doctors-chemotherapists in the RK (2003)



Figure 7 – Staff of the day patient chemotherapy unit, in the center – Candidate of Medical Sciences A.E. Utelbaeva, head of the day patient chemotherapy unit (2010)

In 2011-2012, the RK cancer service came to a new stage of development. The main achievement of KazIOR chemotherapists was the justification of the need to include six targeted drugs in the list of outpatient

anticancer drugs: Lapatinib, Sunitinib, Sorafenib, Imatinib, Erlotinib, and Gefitinib. KZT 3.3 billion was allocated from the Republican budget just for outpatient anticancer therapy. Outpatient chemotherapy offic-

es were opened in every oncological dispensary. The possibility of outpatient treatment, the expansion of access to modern treatment, no need to stay in the hospital to receive drug therapy, and termination of unreasonable interruptions in treatment due to the long queue for hospitalization had a positive impact on therapy effectiveness with metastases in the lungs, kidneys, liver, breast.

Globally, clinical trials are an essential step in drug development that precede drug registration and wide medical use. In clinical trials, a new drug is being studied for effectiveness and safety. The staff of the Chemotherapy Department has participated in many international multicenter clinical trials. Doctors and researchers of the Department participated in clinical trials for the treatment of stomach cancer (under the Soviet-US program of 1975), phase II-III clinical trial of domestic drugs – Gliofen, Arglablin, and Normogen – as part of the international non-interventional study Global Investigation of therapeutic DEcisions in hepatocellular carcinoma [HCC] and Of its treatment with sorafeNib (GIDEON, 2010-2012), phase III international randomized multicenter clinical trial of Cabazi-

taxel with hormone-refractory prostate cancer (CABA-Z\_C\_05331, 2011-2014). Currently, they take part in the randomized, double-blind placebo-controlled phase III multicenter efficacy and safety study of Atezolizumab with triple-negative breast cancer and advanced or metastatic NSCLC (since 2017).

In different years, the staff of KazIOR Chemotherapy Department has defended 12 candidates' theses (A.I. Tsoi, V.A. Fedina, S.K. Kuserbayev, N.A. Chichua, R.R. Valeev, A.O. Turesheva, S.A. Imbergina, S.E. Yessentayeva, K.K. Smagulova, R.Z. Abdrahmanov, A.E. Utelbaeva, A.K. Tumanova) and two doctoral theses (N.A. Chichua, S.E. Yessentayeva), received 16 authors' certificates, published more than 350 scientific papers (more than 45 of them – abroad), issued 14 methodological recommendations.

For many years, a world-renowned chemotherapist, Academician of the Russian Academy of Medical Sciences, Professor, Doctor of Medical Sciences A.M. Garin supervised the activity of the KazIOR Chemotherapy Department and provided constant consultative and methodological assistance in developing treatment tactics for patients.



Figure 8 – Academician of the Russian Academy of Medical Sciences, Professor, Doctor of Medical Sciences A.M. Garin, Doctor of Medical Sciences N.A. Chichua, Candidate of Medical Sciences K.K. Smagulova (2010)

The Department's doctors and staff are constantly improving their qualifications, participating in international and domestic conferences, congresses, and symposia. They authored many papers, monographs, clinical guidelines, and teaching aids. The department doctors are involved in developing Kazakhstan's national clinical guidelines for the treatment of various malignancies, which are run widely used in routine

clinical practice oncologists throughout the Republic of Kazakhstan.

At present, KazIOR Chemotherapy Department is a consulting and methodological center that provides scientific and practical assistance in consolidating the national chemotherapy service. In 2019, Academician of the National Academy of Sciences of the RK, Doctor of Medical Sciences D.R. Kaidarova supported

in arranging international cooperation with the well-known FMI laboratory (USA) on introducing genomic profiling into the RK cancer service.

Chemotherapy Board consults patients according to personified treatment principles based on the tu-

mor molecular-genetic factors identified by new-generation sequencing and integrated genomic profiling (NGS/FMI), organizes monitoring and assessment visits, creates and updates standards for chemotherapeutic treatment of malignant tumors.



Figure 9 – Director of KazIOR, Academician of the National Academy of Sciences of the Republic of Kazakhstan, Doctor of Medical Sciences D.R. Kaidarova with colleagues and representatives of the FMI laboratory (US)

Today, the Chemotherapy Department has the capacity to carry out any modern therapeutic antitumor treatment methods (chemotherapy, endocrine therapy, targeted therapy, immunotherapy). High qualification of doctors, the use of high-quality drugs and consumables, the wide use of relevant concomitant therapy, and close cooperation with international cancer centers allow achieving significant treatment results while maintaining a high quality of life of cancer patients even during the most intensive treatment.

For more than 50 years, the Chemotherapy Department demonstrates a unique symbiosis of science and clinical practice, being a professional and authoritative chemotherapeutic school in Kazakhstan based on a multidisciplinary approach to cancer treatment. Its history and formation still continue, with a long and successful way ahead to fight for the lives of cancer patients.

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## ТҰЖЫРЫМ

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### Қазақ онкология және радиология ҒЗИ химиотерапия бөлімшесінің қалыптасу кезеңдері мен негізгі жетістіктері

Бұл мақала Қазақ онкология және радиология ҒЗИ-дағы химиотерапия бөлімшесіне арналады, ол ҚР онкологиялық науқастарды емдеудегі маңызды буын болып табылады. Онкологиядағы негізгі емдеу әдістерінің бірі ретінде клиникалық химиотерапияның қалыптасуы 1963 жылы, Қазақ онкология және радиология ҒЗИ құрылғаннан кейін үш жылдан кейін институт директоры, профессор С.Н. Нұғмановтың бастамасымен басталды. Емдеу қызметінен басқа, бөлімше қызметкерлері ғылыми-зерттеу жұмыстарымен айналысады, клиникалық зерттеулерге қатысады, елдің химиотерапиялық қызметін шоғырландыруға консультациялық-әдістемелік көмек көрсетеді және қатерлі ісіктерді емдеу бойынша Қазақстандық ұлттық клиникалық ұсынымдарды әзірлеушілері болып табылады.

**Түйінді сөздер:** онкология, химиотерапия, мақсатты терапия, химиотерапия бөлімшесі.

## АННОТАЦИЯ

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### Этапы становления и основные достижения отделения химиотерапии Казахского НИИ онкологии и радиологии

Эта статья об отделении химиотерапии Казахского НИИ онкологии и радиологии, которое является важным звеном в лечении онкологических больных в РК. Становление клинической химиотерапии, как одного из основных методов лечения в онкологии началось в 1963 году, три года спустя после образования Казахского НИИ онкологии и радиологии по инициативе директора института профессор С.Н. Нугманова. Помимо лечебной деятельности, сотрудники отделения занимаются научно-исследовательской работой, участвуют в клинических исследованиях, оказывают консультационно-методическую помощь в консолидации химиотерапевтической службы страны и являются разработчиками казахстанских национальных клинических рекомендаций по лечению злокачественных новообразований.

**Ключевые слова:** онкология, химиотерапия, таргетная терапия, отделение химиотерапии.