MYELODYSPLASTIC SYNDROMES AND IONIZING RADIATION

Summary. The comparative data on the different types of myelodysplastic syndromes (MDS) in Chernobyl clean-up workers and radiation-induced MDS seen in atomic bomb survivors in Japan more than 40 years after exposure are presented. The reasons of long latency of MDS and molecular genetic changes in hematopoietic stem cells are discussed.

Myelodysplastic syndromes (MDS) is heterogeneous group of clonal diseases originating from affection of hematopoietic stem cell (HSC), being accompanied with ineffective hematopoiesis, morphological dysplastic changes, which affect cells of one or several lines of myelopoiesis, increased risk of development of acute myeloid leukaemias (AML). There are MDS, which arise de novo, and secondary MDS developing after use of alkylating chemotherapeutic drugs and/or radiotherapy. Frequency of MDS in all age groups more than in 2 times exceeds incidence of AML [1].

Primary MDS are diagnosed in any age, but prevalently in the old age. Yearly incidence in the most countries of the world constitutes 4.0–5.0 per 100,000 population and increases up to 20.0 per 100,000 in individuals of 60-70 years old. Causes of occurrence of the disease remain completely undetermined. To the etiological factors causing the development of primary MDS are referred benzene, organic solvents, pesticides, series of chemical compounds and other environmental factors [2-4]. Many of these agents are known to be able to induce the development of leukaemias.

Pathognomic for MDS are presence of signs of cytopenia at investigation of peripheral blood, which are accompanied usually with hypercellularity of bone marrow [5]. According with conventional multi-stage model of pathogenesis of MDS, primary is considered caused by genotoxic factors damage and increase of apoptosis stage of actively proliferating HSC. Processes of programmed cellular death are associated with changes of expression in hematopoietic cells of pro- and anti-apoptotic proteins.

In population of CD34-positive blast cells of bone marrow in patients with MDS compared to normal, the ratio of products of expression of oncogenes c-MYC and BCL-2 increases (which enhance apoptosis and improve survival of cells correspondingly). At MDS, the activity of one of the key enzymes of apoptosis— nuclear Ca\(^{++}/\text{Mg}^{++}\)-dependent endonuclease in erythroblast cells is increased. Important role in induction of apoptosis in cells of bone marrow plays system including antigen Fas/Apo (CD95) and its ligand Fas-L, which are detected on the surface membranes at MDS at immunocytochemical study and are determined on the CD34+CD14+ cells in normal. Intensification of apoptosis at MDS is associated with increase of expression of protein p53.

Secondary MDS, like other myeloid tumors (AML, myelodysplastic/myeloproliferative neoplasms) are detected in patients with solid tumors or non-cancer diseases in 5-10 years after chemo- and/or radiotherapy. To the agents, which are able to cause the development of related to the therapy hemoblastosis, are referred alkylating drugs (melphalan, cyclophosphamide, chlorambucil, busulfan, carboplatin, cisplatin, dacarbazine, procarbazine, mytomycin, thiophosphamide, lomustine, etc.), inhibitors of topoisomerase II (etoposide, doxorubicin, mitoxantrone, aktinomycines), antimetabolites (thiopurines, fludarabine, etc.), other drugs (vincristine, vinblastine, hydroxyurea, L-asparaginase, hematopoietic growth factors, radioactive isotopes) [6]. It is assumed that in patients with solid tumors or non-cancer diseases, t-MDS and t-AML occur due to mutations induced by cytotoxic therapy in target cells [4].

Till present time, ideas concerning the role of ionizing radiation in induction of different forms of MDS have been based on the clinical observations, in complex therapy of which quite high-dose radiation has been applied. Significantly lesser data on risk of occurrence of MDS after acute gamma-neutron radiation and long-term action of low doses of ionizing radiation [7,8].
To a certain extent it is conditioned by the fact that different forms of disease are often diagnosed only after 1982, when the French-American-British (FAB) classification of MDS has been proposed [9]. During the next years, classification of MDS has been continuously improved [10].

Modern WHO classification (2008) of MDS allows to allocate the homogeneous subgroups of patients more precisely and has higher prognostic value. It is based on determination of percentage of blasts in bone marrow and peripheral blood and stage of dysplastic changes in one or more of the major myeloid cell lines and data of cytogenetic and molecular-genetic analysis [1].

Classification provides allocation of the following main forms of MDS: refractory cytopenia with unilineage dysplasia (refractory anemia – RA, refractory neutropenia, refractory thrombocytopenia); refractory anemia with ring sideroblasts (RARS); refractory cytopenia with multilineage dysplasia; refractory anemia with excess blasts – (RAEB); MDS unclassifiable; MDS with isolated del(5q); MDS of childhood.

To the most important stochastic effects of ionizing radiation is referred possibility of occurrence of different forms of leukaemias. Latent period of development of AML, acute lymphoblast leukaemia and chronic myelogenous leukaemia dependently on nature and dose of radiation varies between 2-5 years [12]. At MDS, the latent period of development of disease is significantly longer. There are significant biological differences between MDS and AML referring to the probable target cells exposed to radiation, nature of damage, cytogenetic and molecular-genetic abnormalities [12, 13]. Probably, it can explain the fact that till the recent time, researchers had no convincing data concerning the risk of occurrence of MDS even in victims of nuclear explosions in Hiroshima and Nagasaki in 1945 (hibakusha).

In 2011 (60 years after), Japanese researchers have published results of epidemiological study based on the study of two cohorts survived the nuclear bombing in Nagasaki [12]. They studied the database of Atomic Bomb Disease Institute (ABDI) and University of Nagasaki: 64 026 individuals having no information concerning individual doses of radiation, and cohort of affected persons (22245 individuals) with sharply defined individual doses according with DS02, who have been followed-up during the whole life (Life Span Study), in Radiation Effects Research Foundation (RERF).

Diagnostics of forms of MDS (RA, RARS, RAEB, refractory anemia with excess of blasts with transformation – RAEB-T, chronic myelomonocytic leucosis – CMML) has been carried out according with French-American-British classification.

In the first cohort in the period from 1985 to 2004, different forms of MDS have been detected in 151 patients, and in the second – in 47 patients. In the first cohort, the following forms of MDS have been diagnosed: RA – in 20 patients, RARS – in 4, RAEB – in 29, RAEB-T – in 6, CMML and non-classified MDS – in 4 patients. In the second cohort, the RA has been determined in 34 patients, RARS – in 1, RAEB – in 7, RAEB-T – in 3, unclassifiable MDS – in 2 patients. Apparent linear relationship has been determined between occurrence of MDS, being in the moment of explosion within 1.2 km from epicenter or level of received radiation. In the latter case, the index of relative risk of development of the disease in terms of 1.0 Gy has constituted 4.3. Authors have clearly showed that risk of occurrence of radiation-associated MDS persists after 40 years and more after the exposure and is especially high among individuals exposed to radiation in the young age [12].

In the first cohort, the mean period from the moment of exposure to radiation to the occurrence and diagnostics of MDS has constituted 12 years, and in second – 14.4. It should be noticed that the highest frequency of radiation-induced leukaemias at increase of radiation dose has been observed in the first 10-15 years after nuclear bombing. In the future, over time, incidence rates gradually decreased [14].

The assumptions concerning the possibility of development of different forms of MDS, especially among young people suffered from the Chernobyl Nuclear Power Plant catastrophe (CHNPP), have been expressed by us as far as in 1996-1997 [7, 8]. Before the carrying out of large analytical studies in 2002 by group of the USA, France and Ukraine hematopathologists, data, which confirm quite high level of diagnostics of MDS, leukaemias and multiple myeloma in population of Ukraine in 1987-1998, have been published [15]. When carrying out joint Ukrainian-American project for study of radiation risks in 110645 Chernobyl clean-up workers from 4 regions (Chernihiv Oblast, Cherkasy Oblast, Kharkiv Oblast, Kyiv Oblast) and of Kyiv (city) with mean radiation dose 76.4 mGy, different forms of leukaemias have been identified in 87 individuals, and MDS – in 6 [16]. Among clean-up workers, who liquidated the consequences of CHNPP catastrophe of 1986-1987 from Belarus Republic, Russian Federation and Baltic States, with reconstructed dose of radiation, 117 patients with hemoblastosis have been diagnosed, including 2 patients with MDS [18]. In the Department of Hematology of Hospital of Scientific Center of Radiation Medicine of NAMS of Ukraine, 45 patients with received mean dose of radiation 4.90-67.86 Sv/s, in whom according with 2001 WHO classification, have been diagnosed such forms of MDS, as RA, RARS, RAEB, RAEB-T, CMML, were on treatment in different time [17].

Latent period of development of MDS in people, who have survived nuclear bombing in Hiroshima and Nagasaki, is longer than at AML, and approximates to the terms of occurrence of solid tumors [19]. It is assumed that nature of genetic damages of HSC, and molecular mechanisms of development of mentioned diseases can be different. In Hiroshima residents with MDS, who have survived nuclear bombing, high level of point mutations of suppressor oncogene p53 has been determined [20]. In this regard, data concerning high frequency of point mutations in gene AML1/RUNXI, arising under the action of low radiation doses, attract special attention. They have been registered in 6 (46%) out of 13 patients with MDS – residents of Hiroshima. Such
mutations have been detected in patients with MDS/AML, which developed after radiation therapy. Frequency of mutations in patients with sporadic MDS was significantly lower (2.7%) [21]. Quite high (39%) correlating with radiation dose level of mutations in gene AML1/RUNXI has been determined at radiation-associated MDS in individuals, who have been residing near Semipalatinsk testing area [22]. Authors assume that point mutations in gene AML1 may be used as biomarker for differentiation of radiation-induced and spontaneously arising MDS/AML.

In established on the basis of Department of Immunocytochemistry and Oncohematology of the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine of reference laboratory in the period of 1996-2010, the diagnostics of oncohematologic diseases in Chernobyl clean-up workers has been conducted [23]. According to the official statistics, the cohort of people in Ukraine, who directly participated in liquidation of consequences of Chernobyl disaster in 1986, has constituted 260870 people (mean dose of radiation 140 mGy) and in 1987 – 43366 people (mean dose of radiation 90 mGy).

Totally 295 clean-up workers with tumor diseases of hematopoietic and lymphoid tissue have been examined (acute myeloid and lymphoid leukaemias, chronic myelogenous leukaemia, chronic lymphocytic leukaemia, B- and T-cell non-Hodgkin’s lymphomas in the leukemization phase, multiple myeloma, MDS). In this group, different forms of MDS have been diagnosed in 16 (5.42%) patients, while in group of 2697 people not exposed to radiation – in 107 (3.70%). In the next years (2007-2012), MDS have been diagnosed in 4 clean-up workers. Age of patients (18 men and 2 women) varied from 33 to 78 and has constituted in average 62. According to 2008 WHO classification, RA classification, RA has been detected in 11 patients, RARS – in 2, refractory anemia with excess of blasts – in 7 (RAEB-1 and RAEB-2). MDS have been detected in 2 clean-up workers in 1997, in 3 – in 1998, in 3 – in 1999, in 2 – in 2000, in 2 – in 2001, by 1 case in 2002-2005.

It is also interesting that in 10 (3.39%) patients, who were under observation in 1996-2010, CMML has been diagnosed, which previously considered to be one of the MDS forms [10], and currently is referred to the category of myelodysplastic/myeloproliferative neoplasms [11]. Unit weight of CMML among oncohematologic diseases in individuals, who were not exposed to radiation, has constituted 3.11% [23]. Moreover, it should be mentioned that in 7 (15.2%) out of 46 clean-up workers with AML, different cytological variants have been detected, which were referred to the category of AML with myelodysplasia related changes (AML with minimal signs of differentiation, acute myelomonocytic leukaemia and acute erythroleukaemia). Among individuals not exposed to ionizing radiation, AML with myelodysplasia related changes have been registered in 1.5% of cases.

Thus, case of Hiroshima and Nagasaki and the results of examination of CHNPP disaster clean-up workers allow to recognize that development of MDS, the same as other forms of tumor disease of hematopoietic and lymphoid tissues, may be connected with ionizing radiation despite different origin, duration of exposure and level of received dose.

Different forms of MDS, which arise at that, probably, shall be referred to secondary ones, similar to those, which develop in the result of use of alkylating drugs and/or radiation therapy. Relevant is the issue concerning cells-targets and mechanisms, which underlie the development of MDS associated with ionizing radiation.

REFERENCES


