CLINICAL, ECONOMICAL AND ETHICAL ASPECTS ASSESSING THERAPY OUTCOMES IN PATIENTS WITH MULTIPLE MYELOMAS OF HIGH CYTOGENETIC RISK

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According to European authors, patients with multiple myeloma (MM) and high cytogenetic risk have shorter values of progression free survival (PFS) and overall survival (OS) as compared with standard hazard. More frequent hospitalizations mean potentially high expenses associated with management of patients with unfavorable cytogenetic risk. Cost and availability of treatment of oncological patients relate to one of pressing ethical issues. Another important aspect of this issue consists in an effective use of available approved modes of therapy in patients with various survival prognosis, which is especially critical for early lines of therapy. It has been proven that early administration of more effective modes based on individual characteristics both of a patient, and a disease will improve the total survival of patients. This will result in reduction of economic resources spent on selecting new modes of treatment in patients with a disease recurrence and correction of possible adverse effects and hospitalization.

Key words: multiple myeloma, cytogenetic risk, clinical and economical assessment, ethical issues, overall survival, hospitalizations

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КЛИНИКО-ЭКОНОМИЧЕСКИЕ И ЭТИЧЕСКИЕ АСПЕКТЫ ОЦЕНКИ ИСХОДОВ ТЕРАПИИ ПАЦИЕНТОВ С МНОЖЕСТВЕННОЙ МИЕЛОМОЙ ВЫСОКОГО ЦИТОГЕНЕТИЧЕСКОГО РИСКА

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По данным европейских авторов, у пациентов с множественной миеломой (ММ) с высоким цитогенетическим риском наблюдаются значительно более короткие значения беспрогрессивной (ВБП) и общей выживаемости (ОВ) по сравнению со стандартным риском. Более частые госпитализации указывают на потенциально высокие расходы, связанные с ведением пациентов с неблагоприятным цитогенетическим риском. Стоимость и доступность лечения онкологических пациентов являются одним из актуальных этических вопросов. Другой важный аспект этой проблемы это эффективное применение существующих одобренных схем терапии у пациентов с различным прогнозом по выживаемости, что особенно критично в ранних линиях терапии. Доказано, что назначение более эффективных режимов как можно раньше в соответствии с индивидуальными особенностями и пациента и заболевания будет способствовать увеличению в итоге общей выживаемости больных. Как результат позволит сократить экономические ресурсы, которые тратятся на выбор новых схем у пациента с рецидивом заболевания, а также на коррекцию возможных побочных эффектов, госпитализации.

Ключевые слова: множественная миелома, цитогенетический риск, клинико-экономическая оценка, этические вопросы, общая выживаемость

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Multiple myeloma (MM) is currently one of the most widely spread malignant vascular system tumors and, in spite of a significant number of accessible therapeutic options, patients' outcomes require improvement [1].

In patients with MM, various cytogenetic and molecular genetic breakages of tumor cells are met rather frequently and determined as the most important factors influencing the course and prognosis of MM (table 1) [2]. Depending on the effect produced on survival, high risk cytogenetic disturbances are detected (resulting in reduced overall survival) [1].

Determination of a high-risk myeloma has evolved over time and includes cytogenetic and clinical biomarkers (table 2) [3].

Due to a rather bad prognosis in a high-risk disease, there still remains a purpose of developing new treatment options for patients from a high-risk group. Thus, it's important to provide clear recommendations related to treatment of high-risk multiple myeloma to improve general therapy outcomes. The simplest approach to risk stratification is represented by the International Staging Scale that uses two available laboratory values (serum β2 microglobulin and serum albumin) (table 2) [3].

For a more exact prognosis, tumor load (stage) and disease biology (presence of molecular and genetic high-risk pathologies or increased level of LDH) should be assessed. The factors are estimated within the reviewed staging system (R-ISS) to develop a single prognostic index. To ensure consistency, only widely accepted cytogenetic markers such as trisomy, t (11;14), t (6;14), t (4;14), t (14;16), t (14;20), del 17p, + 1q are used in R-ISS [4]. The model of risk stratification called Mayo stratification (mSMART) and developed at Mayo clinic, which divides patients into two groups with high and standard risks, provides additional information for prognosis and selection of a therapeutic strategy (table 3) [5].

The prognostic value of (high-risk) cytogenetic abnormalities in MM is evident (table 4) [5, 6]. However, limited data of real practice (mainly of European origin) are currently available. They describe clinical and economical models of treatment and

Table 1. Incidence of various cytogenetic abnormalities (adapted by Abdallah et al. 2020) [2]

Cytogenetic abnormalities	N (tested patients)	N (%) with cytogenetic abnormalities
IgH translocation with trisomy	1959	312 (16)
t (11;14)	1962	58 (3)
t (4;14)	1961	60 (3)
t (14;16)	1961	23 (1)
t (6;14)	1962	9 (<1)
t (14;20)	1962	6 (<1)
Unknown deletion of IgH	1959	156 (8)
IgH translocation without trisomy	1959	581 (30)
t (11;14)	1962	315 (16)
t (4;14)	1961	117 (6)
t (14;16)	1961	55 (3)
t (6;14)	1962	9 (<1)
t (14;20)	1962	14 (<1)
Unknown deletion of IgH	1959	71 (4)
Trisomy without IgH translocation	1959	791 (40)

Table 2. MM staging based on ISS and R-ISS (adapted by Palumbo A et al. J Clin Oncol. 2015;33(26):2863–2869.) [3]

R-ISS	stage I	stage II	stage III
ISS	Serum β_2-microglobulin <3.5 mg/l; albumin ≥3.5 g/dl)	Not R-ISS stages I or III	Serum β_2- microglobulin ≥5.5 mg/l)
Cytogenetic disturbances (CD)	Standard risk*		High risk of CD** or high LDH (<above the normal interval)
LDH	Normal (<above the normal interval)		
	5-year OS (%)		
	82%†	62%†	40%†

* Lack of del(17p) mutation and/or t(4;14)(p16;q32) translocation and/or t(14;16)(q32;q23) translocation.
** Presence of del(17p) and/or t(4;14)(p16;q32) translocation and/or t(14;16)(q32;q23) translocation.
† In general population of 4445 patients with a mean age of 62 years, 60% received auto-HSCT (the majority were ≤65), 44% obtained proteosome inhibitors, 66% received immunomodulators, 5% obtained no novel agents. 871 patients developed (28%) R-ISS stage I, 295 (10%) R-ISS stage III, and 1894 (62%) R-ISS stage II.

Table 3. Classification of mSMART in MM [4]

Risk group	Stratification criteria	Treatment approaches
High	– High risk genetic abnormalities t(4;14) t(14;16) t(14;20) Del 17p p53 mutation + 1q R ISS stage 3 – High amount of plasma cells in S-phase (synthesis) – Gene expression profile (GEP): high risk	– Aggressive and continuous therapy – Triple-combination
Standard	All the rest including: – trisomy – t(11;14)[d] – t(6;14)	– Treatment-free intervals can be useful to get a minimal number of toxic therapy effects. – Triple combined therapy is preferable.

Adapted from mSMART Mayo Stratification for Myeloma and Risk-adapted Therapy Newly Diagnosed Myeloma. V14. Accessed January 24, 2019. https://www.msmart.org/mm-treatment-guidelines.

outcomes for patients with MM with high cytogenetic risk. Results of international randomized clinical trials presenting effectiveness of novel agents and their combinations in patients with different cytogenetic risks are published (table 5) [7]. It is shown that some regimens are able to overcome the high cytogenetic risk and increase overall survival of patients with MM.

Results of retrospective analysis of 200 patients with MM recurrence risk in France have been published [8]. Outcomes of patients during second-line therapy were estimated after the first recurrence. 192 patients (96%) obtained second-line therapy following the recurrence: the most widely used regimens included lenalidomide (>50%). The rate of hospitalization was approximately twice higher among patients with high risk as compared with patients with standard risk. Based on Kaplan-Meier estimator, median (95% CI) of second-line progression-free survival (PFS) was 21.4 (17.5, 25.0) months

Table 4. Comparison of tests using ISS and FISH-based prognostic models [5, 6]

	IMWG	MRC	Немецкое исследование
Treatment	Includes both young (transplant candidates) and elderly patients (chemotherapy only)	Young (intensive) and older patients (non-intensive) with thalidomide-based combination at induction and thalidomide maintenance on MRC IX trials	Chemo-based induction followed by HD Mel ASCT and maintenance
N	2637	629	315
Low risk			
Parameter	ISS* I/II, no adverse FISH abnormalities†	ISS I/II, no adverse FISH abnormalities‡; ISS I, 1 adverse FISH abnormality	ISS I, no adverse FISH abnormalities†
% of patients	51%	38%	42%
OS	76% during 4 years	Median of 67.8 months	72% during 5 years
Intermediate risk			
Parameter	ISS III, no adverse FISH abnormalities; ISS I, t(4;14)/del(17p13)	ISS I, >1 adverse FISH abnormality; ISS II/III, 1 adverse FISH abnormality; ISS III, no adverse FISH abnormalities	ISS II/III, no adverse FISH abnormalities; ISS I, t(4;14)/del(17p13)
% of patients	29%	48%	44%
OS	45% during 4 years	Median of 41.3 months	62% during 5 years
High risk			
Parameter	ISS II/III, t(4;14)/del(17p13)	ISS II/III, >1 adverse FISH abnormalities	ISS II/III, t(4;14)/del(17p13)
% of patients	20%	14%	14%
OS	33% during 4 years	Median of 19.4 months	41% during 5 years

* ISS stage I, β2-microglobulin <3.5 mg/l and albumin ≥3.5 g/dl; ISS stage III, β2-microglobulin ×5.5 mg/l; ISS stage II, not ISS or ISS III.
† Adverse FISH displacement t(4;14) and/or del(17p13).
‡ Adverse FISH adverse IgH translocation [t(4;14) or t(14;16) or t(14;20)], del(17p13), and/or 1q2

Table 5. Outcomes for patients depending on cytogenetic risk in newly detected MM (adapted by Caro J. et al. 2021) [7]

Test	Regimen	Design	Examined risk	Number of patients with high risk	Primary outcome measure	Results
SWOG-1211[21]	Elotuzumab-VRd vs VRd	Phase II, high risk only, not auto-HSCT candidates	Expression of high risk genes, t(14;16), t(14;20), del (17p), amp (1q21), high levels of LDH, PCL	100 (100)	PFS	31.5 vs 33.6 months p=0.45
SWOG S077[22,23]	VRd vs Rd	Phase III, not auto-HSCT candidates	t(4;14), t(14;16), del (17p)	44 (8)	PFS	38 vs 16 months P=0.19
ALCYONE[24]	Dara-VMP vs VMP	Phase III, not auto-HSCT candidates	t(4;14), t(14;16), del (17p)	98 (14)	PFS	18 vs 18.1 (not significant)
MAIA[25]	Dara-Rd vs Rd	Phase III, not auto-HSCT candidates	t(4;14), t(14;16), del (17p)	92 (12)	PFS	Not assessed, not significant
CASSIOPEIA[26]	Dara-VTd vs VTd	Phase III, auto-HSCT candidates	t(4;14), del (17p)	168 (15)	sCR in 100 days after auto-HSCT	24% vs 28%, not significant
GRIFFIN[27]	Dara-VRd vs VRd	Phase III, auto-HSCT candidates	t(4;14), t(14;16), del (17p)	30 (14)	sCR after consolidation	18,8% vs 30,8%, not significant
STAMINA[28,29]	Ауто-ТГСК +Rd supportive + VRd consolidation+Rd supportive vs tandem auto-HSCT +Rd supportive.	Phase III, auto-HSCT candidates	в2>5,5 mg/l, t(4;14), t(14;16), del (17p), t (14,20), del (13) or aneuploidy	223(29)	sCR in 38 months	57,6% vs 61,6% vs 62,9%, p not available value
EMN 02/H095[30,31]	VCD, VMP vs auto-HSCT (solitary or double)	Phase III, auto-HSCT candidates	t(4;14), t(14;16), del (17p)	225 (19)	sCR	20,3 vs 37,3 months, HR 0,63 (95CI, 046–0,88)

Abbreviations: VRd, bortezomib, lenalidomide, dexamethasone; PCL, plasma cell leukemia; LDH — lactate dehydrogenase; PFS, progression-free survival; Rd lenalidomide, dexamethasone; Dara, daratumumab; VMP, bortezomib, melphalan, prednisolone; VTd, bortezomib, thalidomide, dexamethasone; sCR, stringent complete response; auto-HSCT — autologous stem cell transplantation, в2 — beta-2 microglobulin; VCD — bortezomib, cyclophosphamide, dexamethasone; HR — hazard ratio

(as compared with standard risk: 10.6 [6.4, 17,0] vs 28.7 [22.1, 37.3] months). Median of second-line overall survival (OS) was 59.4 (38.8, NE) months (high risk as compared with standard one: 36.5 [17.4, 50.6] vs 73.6 [66.5, NE] months).

Among patients who initiated second-line treatment with bortezomib, third-line therapy with lenalidomide was the most widely spread regimen. Relatively small number of patients received bortezomib during third-line therapy after withdrawal of lenalidomide during the second-line therapy. The majority of patients cancelled treatment (*n* = 176.92%) by the moment when the study was completed. The principal reasons were disease progression (37%), lack of maximum response without expected additional profit (33%), and loss of response (13%). Duration of second-line treatment is commonly less than one year. It displays not satisfactory results for this line of therapy and requires to select a therapy regimen for every separate patient considering cytogenetic risk, starting from first-line therapy.

Thus, patients with high cytogenic risk had shorter values of PFS and OS as compared with standard one. More frequent hospitalization meant potentially high expenses associated with management of patients with high genetic risk. The data show that systemic collection and analysis of results obtained during the Russian real clinical practice of treatment of patients with MM are necessary for subsequent clinical and economical assessment of therapy outcomes in patients with high cytogenic risk of MM recurrence and possible correction of first-line treatment regimens.

Multiple myeloma is an incurable disease. Implementation of novel drugs into practice resulted in a significantly improved survival in the presence of multiple myeloma. This is associated with implementation of novel agents (proteasome inhibitors such as carfilzomib and ixazomib; monoclonal antibodies such as daratumumab and elotuzumab) into clinical practice [9–13]. In addition to new regimens, regimens with two medicinal agents used within a limited period of time, are increasingly replaced with regimens consisting of three or four medicinal preparations continuously used until progression. This improves survival even more [14]. Within 5 years, expected survival almost doubled from 38% in 1989–2000 to 64% in 2008–2016.

Some novel drugs and their combinations display high effectiveness in patients with high cytogenetic risk. However, a lack of recommendations regarding different therapy regimens depending on cytogenetic risk is a serious problem both for doctors, and for patients with myeloma.

Implementation of novel agents and improved overall survival result in higher expenses on treatment of oncological patients [15, 16].

The growing expenses are only partially associated with the incidence rate [17]. As compared with medicinal agents used for other indications, oncological drugs are more costly in absolute and relative terms [18]. These growing expenses cause concern as they compromise availability of effective therapy for patients.

For instance, among patients newly diagnosed with MM in the USA, healthcare expenditure per one patient a month increased from 3,263 US dollars in 2000 to 14,656 US dollars in 2014 [19].

Clinical and economical aspects of treatment of patients with MM raise a number of ethical questions. Cost of therapy is one of them. Providing treatment to people with limited resources forms the basis of any healthcare system. Growing worldwide cost of drug therapy of oncological diseases combined with insufficiently effective therapy outcomes raise questions about how effectively the existing therapy regimens are used in patients with different survival prognosis. This is especially true for early therapy lines because administration of more effective regimens based on individual characteristics both of the patient, and the disease, will sooner or later contribute to increased overall survival of patients. In future, this will reduce economical resources spent on selection of new regimens for a patient with disease recurrence, and correction of possible adverse effects and hospitalization.

For instance, the mean assumed threshold of economical effectiveness among oncologists was 280,000 US dollars per quality-adjusted life year (QALY). It is much higher than 50,000 US dollars per QALY regularly used by healthcare experts [20]. At least one oncologist in this study noted that addition of one day of life would justify expenses in the amount of 70,000 US dollars per year which is equivalent to 25 mln US dollars per QALY.

At disease onset, assessment of prognostic factors (including pathogenetic risk) in a patient with MM should be of fundamental importance while selecting therapy and will ultimately promote better overall survival. It will reduce a number of hospitalizations and expenses on correction of adverse events. Implementation of novel agents into clinical practice and increased cost of management of patients with oncological diseases (including the ones with multiple myeloma) raise ethical issues of therapy availability and need of patients in the most effective regimens based on their individual and disease characteristics.

References

1. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016; 127: 2955–2962.
2. Abdallah N, Rajkumar SV, Greipp P, Kapoor P, Gertz MA, Dispenzieri A, Baughn LB, Lacy MQ, Hayman SR, Buadi FK, Dingli D, Go RS, Hwa YL, Fonder A, Hobbs M, Lin Y, Leung N, Kourelis T, Warsame R, Siddiqui M, Lust J, Kyle RA, Bergsagel L, Ketterling R, Kumar SK. Cytogenetic abnormalities in multiple myeloma: association with disease characteristics and treatment response. Blood Cancer J. 2020 Aug 11; 10 (8): 82. DOI: 10.1038/s41408–020–00348–5. PMID: 32782240; PMCID: PMC7419564.
3. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol. 2005; 23: 3412–3420.
4. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BG, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015 Sep 10; 33 (26): 2863–9. DOI: 10.1200/JCO.2015.61.2267. Epub 2015 Aug 3. PMID: 26240224; PMCID: PMC4846284.
5. Mayo Clinic. (2021). Mayo stratification for myeloma and risk-adapted therapy: relapsed myeloma. Available from mSMART: A clear and simple guide for treating patients with multiple myeloma — Mayo Clinic (Accessed 9 December 2021).
6. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, Munshi N, Palumbo A, Miguel JS, Sonneveld P, Cavo M, Usmani S, Durie BG, Avet-Loiseau H; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014 Feb; 28 (2): 269–77. DOI: 10.1038/leu.2013.247. Epub 2013 Aug 26. PMID: 23974982.
7. Caro J., Al Hadidi S, Usmani S, Yee A, Raje N, Davies F. How to Treat High-Risk Myeloma at Diagnosis and Relapse DOI: 10.1200/

EDBK_320105 American Society of Clinical Oncology Educational Book. May 19, 2021; 41: 291–309.
8. Lin HM, Davis KL, Kaye JA, Luptakova K, Nagar SP, Mohty M. Real-World Treatment Patterns, Outcomes, and Healthcare Resource Utilization in Relapsed or Refractory Multiple Myeloma: Evidence from a Medical Record Review in France. Adv Hematol. 2019 Jan 29; 2019: 4625787. DOI: 10.1155/2019/4625787. PMID: 30838045; PMCID: PMC6374830.
9. Orlowski RZ, Moreau P, Niesvizky R, Ludwig H, Oriol A, Chng WJ, Goldschmidt H, Yang Z, Kimball AS, Dimopoulos M. Carfilzomib-Dexamethasone versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups. Clin Lymphoma Myeloma Leuk. 2019; 19: 522–530.e1.
10. Dimopoulos M, Quach H, Mateos MV, Landgren O, Leleu X, Siegel D, Weisel K, Yang H, Klippel Z, Zahlten-Kumeli A, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): Results from a randomised, multicentre, open-label, phase 3 study. Lancet 2020; 396: 186–197.
11. Richardson, P.G.; Kumar, S.K.; Masszi, T.; Grzasko, N.; Bahlis, N.J.; Hansson, M.; Pour, L.; Sandhu, I.; Ganly, P.; Baker, B.W.; et al. Final Overall Survival Analysis of the TOURMALINE-MM1 Phase III Trial of Ixazomib, Lenalidomide, and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma. J Clin Oncol Off. J Am Soc Clin Oncol. 2021; 39: 2430–2442.
12. Bahlis NJ, Dimopoulos MA, White DJ, Benboubker L, Cook G, Leiba M, Ho PJ, Kim K, Takezako N, Moreau P, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia 2020; 34: 1875–1884.
13. Dimopoulos MA, Lonial S, Betts KA, Chen C, Zichlin ML, Brun A, Signorovitch JE, Makenbaeva D, Mekan S, Sy O, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. Cancer. 2018; 124: 4032–4043.
14. Roy A, Kish JK, Bloudek L, Siegel DS, Jagannath S, Globe D, Kuriakose ET, Migliaccio-Walle K. Estimating the Costs of Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma: A Model Framework. Am Health Drug Benefits. 2015; 8: 204–215.
15. International Monetary Fund (IMF). SDRs per Currency Unit for July 2021. Available online: https://www.imf.org/external/np/ fin/data/rms_mth.aspx? SelectDate=2021–07–31&reportType=SDRCV (accessed on 13 August 2021).
16. Hofmarcher T, Lindgren P, Wilking N, Jönsson B. The cost of cancer in Europe 2018. Eur J Cancer. 2020; 129: 41–49.
17. World Health Organization. Pricing of Cancer Medicines and Its Impacts; World Health Organization: Geneva, Switzerland, 2018. Available online: https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?sequence=1&isAllowed=y (accessed on 10 April 2020).
18. Cook R. Economic and clinical impact of multiple myeloma to managed care. J. Manag. Care Plus Spec Pharm. 2008; 14: 19–25.
19. Fonseca R, Abouzaid S, Bonafede M, Cai Q, Parikh K, Cosler L, Richardson P. Trends in overall survival and costs of multiple myeloma, 2000–2014. Leukemia. 2017; 31: 1915–1921.
20. Nadler E, Eckert B, Neumann P. Do oncologists believe new cancer drugs offer good value? The Oncologist. 2006; 11: 90–5.
21. Usmani SZ, Hoering A, Ailawadhi S, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. Lancet Haematol. 2021; 8: e45-e54.
22. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020; 10: 53.
23. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017; 389: 519–527.
24. Mateos M–V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018; 378: 518–528.
25. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019; 380: 2104–2115.
26. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019; 394: 29–38.
27. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020; 136: 936–945.
28. Hari P, Pasquini MC, Stadtmauer EA, et al. Long-term follow-up of BMT CTN 0702 (STAMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). J Clin Oncol. 2020; 38(suppl; abstr 8506).
29. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial. J Clin Oncol. 2019; 37: 589–597.
30. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomiblenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020; 7: e456– e468.
31. Sonneveld P, Beksac M, Van Der Holt B, et al. Consolidation treatment with VRD followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant-eligible patients with multiple myeloma (MM): a randomized phase 3 trial of the European Myeloma Network (EMN02/HO95). Blood. 2020; 136(suppl): 46–48.

Литература

1. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016; 127: 2955–2962.
2. Abdallah N, Rajkumar SV, Greipp P, Kapoor P, Gertz MA, Dispenzieri A, Baughn LB, Lacy MQ, Hayman SR, Buadi FK, Dingli D, Go RS, Hwa YL, Fonder A, Hobbs M, Lin Y, Leung N, Kourelis T, Warsame R, Siddiqui M, Lust J, Kyle RA, Bergsagel L, Ketterling R, Kumar SK. Cytogenetic abnormalities in multiple myeloma: association with disease characteristics and treatment response. Blood Cancer J. 2020 Aug 11; 10 (8): 82. DOI: 10.1038/s41408–020–00348–5. PMID: 32782240; PMCID: PMC7419564.
3. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol. 2005; 23: 3412–3420.
4. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BG, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015 Sep 10; 33 (26): 2863–9. DOI: 10.1200/JCO.2015.61.2267. Epub 2015 Aug 3. PMID: 26240224; PMCID: PMC4846284.

5. Mayo Clinic. (2021). Mayo stratification for myeloma and risk-adapted therapy: relapsed myeloma. Available from mSMART: A clear and simple guide for treating patients with multiple myeloma — Mayo Clinic (Accessed 9 December 2021).
6. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, Munshi N, Palumbo A, Miguel JS, Sonneveld P, Cavo M, Usmani S, Durie BG, Avet-Loiseau H; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014 Feb; 28 (2): 269–77. DOI: 10.1038/leu.2013.247. Epub 2013 Aug 26. PMID: 23974982.
7. Caro J., Al Hadidi S, Usmani S, Yee A, Raje N, Davies F. How to Treat High-Risk Myeloma at Diagnosis and Relapse DOI: 10.1200/EDBK_320105. American Society of Clinical Oncology Educational Book. May 19, 2021; 41: 291–309.
8. Lin HM, Davis KL, Kaye JA, Luptakova K, Nagar SP, Mohty M. Real-World Treatment Patterns, Outcomes, and Healthcare Resource Utilization in Relapsed or Refractory Multiple Myeloma: Evidence from a Medical Record Review in France. Adv Hematol. 2019 Jan 29; 2019: 4625787. DOI: 10.1155/2019/4625787. PMID: 30838045; PMCID: PMC6374830.
9. Orlowski RZ, Moreau P, Niesvizky R, Ludwig H, Oriol A, Chng WJ, Goldschmidt H, Yang Z, Kimball AS, Dimopoulos M. Carfilzomib-Dexamethasone versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups. Clin Lymphoma Myeloma Leuk. 2019; 19: 522–530.e1.
10. Dimopoulos, M, Quach, H, Mateos, M.V, Landgren, O, Leleu, X, Siegel, D, Weisel, K, Yang, H, Klippel, Z, Zahlten-Kumeli, A, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): Results from a randomised, multicentre, open-label, phase 3 study. Lancet 2020, 396, 186–197.
11. Richardson PG, Kumar SK, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, Sandhu I, Ganly, P, Baker BW, et al. Final Overall Survival Analysis of the TOURMALINE-MM1 Phase III Trial of Ixazomib, Lenalidomide, and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma. J Clin Oncol Off J Am Soc Clin Oncol. 2021; 39: 2430–2442.
12. Bahlis NJ, Dimopoulos MA, White DJ, Benboubker L, Cook G, Leiba M, Ho PJ, Kim K, Takezako N, Moreau P, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia. 2020; 34: 1875–1884.
13. Dimopoulos MA, Lonial S, Betts KA, Chen C, Zichlin ML, Brun A, Signorovitch JE, Makenbaeva D, Mekan S, Sy O, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. Cancer. 2018; 124: 4032–4043.
14. Roy, A, Kish, J.K, Bloudek, L, Siegel, D.S, Jagannath, S, Globe, D, Kuriakose, E.T, Migliaccio-Walle, K. Estimating the Costs of Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma: A Model Framework. Am. Health Drug Benefits. 2015, 8, 204–215.
15. International Monetary Fund (IMF). SDRs per Currency Unit for July 2021. Available online: https://www.imf.org/external/np/ fin/data/rms_mth.aspx? SelectDate=2021–07–31&reportType=SDRCV (accessed on 13 August 2021).
16. Hofmarcher T, Lindgren P, Wilking N, Jönsson B. The cost of cancer in Europe 2018. Eur J Cancer. 2020; 129: 41–49.
17. World Health Organization. Pricing of Cancer Medicines and Its Impacts; World Health Organization: Geneva, Switzerland, 2018. Available online: https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?sequence=1&isAllowed=y (accessed on 10 April 2020).
18. Cook R. Economic and clinical impact of multiple myeloma to managed care. J Manag Care Plus Spec Pharm. 2008; 14: 19–25.
19. Fonseca R, Abouzaid S, Bonafede M, Cai Q, Parikh K, Cosler L, Richardson P. Trends in overall survival and costs of multiple myeloma, 2000–2014. Leukemia. 2017; 31: 1915–1921.
20. Nadler E, Eckert B, Neumann P. Do oncologists believe new cancer drugs offer good value? The Oncologist. 2006; 11: 90–5.
21. Usmani SZ, Hoering A, Ailawadhi S, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. Lancet Haematol. 2021; 8: e45-e54.
22. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020; 10: 53.
23. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017; 389: 519–527.
24. Mateos M–V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018; 378: 518–528.
25. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019; 380: 2104–2115.
26. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019; 394: 29–38.
27. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020; 136: 936–945.
28. Hari P, Pasquini MC, Stadtmauer EA, et al. Long-term follow-up of BMT CTN 0702 (STAMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). J Clin Oncol. 2020; 38(suppl; abstr 8506).
29. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial. J Clin Oncol. 2019; 37: 589–597.
30. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomiblenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020; 7: e456-e468.
31. Sonneveld P, Beksac M, Van Der Holt B, et al. Consolidation treatment with VRD followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant-eligible patients with multiple myeloma (MM): a randomized phase 3 trial of the European Myeloma Network (EMN02/HO95). Blood. 2020; 136(suppl): 46–48.