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Dose-reduction trials in oncology — aiming for less toxicity and better quality of life at lower costs

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Supplementary Table 1 | Examples of clinical studies investigating cancer drug dose-reduction strategies

Drug; indication	Label dose	Lower effective dose	Extent of dose reduction	Calculated drug costs reductions (total drug costs) for 100 patients per completed course of treatment or 1 year of treatment (€)[a]			
				Denmark	UK	Germany	USA
Gemtuzumab; AML	3 mg/m^2 IV on days 1, 4 and 7 of cycle 1 and day 1 of cycle 2, in combination with chemotherapy	3 mg/m^2 IV on day 1 of cycle 1, in combination with chemotherapy[1]	75%	2,455,818 (3,274,424)	2,198,070 (2,930,760)	2,499,300 (3,332,400)	2,826,340 (3,766,500)
Nivolumab; various, including melanoma, NSCLC and RCC	3 mg/kg IV every 2 weeks	0.1–0.3 mg/kg IV every 2 weeks[2]	>90%	8,761,188 (9,734,644)	7,157,335 (7,952,594)	7,319,600 (8,132,800)	16,943,991 (18,826,993)
	Flat dose 480 mg IV every 4 weeks or 240 mg IV every 2 weeks	Flat dose 480 mg IV every 8 weeks[3]	50%	4,867,322 (9,734,644)	3,976,297 (7,952,594)	3,976,297 (8,132,800)	9,413,318 (18,826,993)
Ibrutinib; CLL	420 mg PO QD	140 mg PO QD[4–6]	66% Reductions in platelet inhibition and bleeding observed	6,285,042 (9,080,872)	4,324,034 (6,486,051)	5,021,900 (7,607,600)	11,037,289 (16,555,887)
	Cycles 1–15 (each lasting 28 days): all patients 420 mg PO QD plus venetoclax 400 mg PO QD during cycles 3–15 From cycle 16: MRD-positive patients (65%) received continuous maintenance ibrutinib 420 mg PO QD; MRD-negative patients (35%) were randomized to continuous ibrutinib or cessation of treatment with MRD-guided treatment re-initiation of ibrutinib plus venetoclax	MRD-guided omission of maintenance ibrutinib and treatment re-intiation[7]	100% for MRD-negative patients (that is, 35% of all patients after cycle 15). 2% of patients had ibrutinib re-initiation during cycles 16–27, and 15% had ibrutinib re-initiation during cycles 28–40. Reductions of severe adverse events, including infections, neutropenia, gastrointestinal adverse events, was observed.	9,080,872 (9,080,872)	6,486,051 (6,486,051)	7,607,600 (7,607,600)	16,555,887 (16,555,887)
Imatinib; CML	400 mg PO QD	MRD-guided drug withdrawal and and re-intiation at loss of CMR[8]	100% for CML patients in CMR after mean follow-up duration of 23 months (51% of patients)	2,908,189 (2,908,189)	2,597,909 (2,597,909)	4,277,800 (4,277,800)	1,858,080 (1,858,080)
Trastuzumab; HER2$^+$ breast cancer	12-months treatment plus chemotherapy, either 8 mg/kg IV loading dose and 6 mg/kg IV maintenance doses every 3 weeks, or flat dose of 600 mg SC every 3 weeks	6-months treatment plus chemotherapy as per label doses[9]	50% Reduction of adverse events, including cardiotoxicity, observed	1,621,574 (3,243,135)	4,408,817 (8,817,633)	2,599,600 (5,199,100)	5,393,076 (10,786,356)

Decitabine; AML, MDS, CMML and PMF	20 mg/m^2 SC QD on days 1–5 every 4 weeks	3.5–5 mg/m^2 every week[10]	>80% Active DNMT1 inhibition and reduction of cytotoxic effects demonstrated	7,772,590 (9,244,928)	NA	6,781,400 (8,073,000)	9,657,942 (11,497,723)
Certinib; *ALK*-rearranged NSCLC	750 mg PO QD during fasting period	450 mg PO QD with food[11,12]	40% Reduction of GI adverse events observed	3,244,529 (8,092,689)	2,786,432 (6,965,905)	4,464,300 (11,160,800)	10,372,739 (25,941,410)
Abiraterone; prostate cancer	1,000 mg PO QD during fasting period	250 mg PO QD with food[13]	75%	3,409,188 (4,545,575)	2,440,904 (3,254,423)	3,651,600 (4,868,800)	9,742,151 (12,989,780)
Mean	–	–	**72%**	**5,040,631** **(6,893,997)**	**4,041,761** **(5,938,213)**	**4,828,950** **(6,839,270)**	**9,380,081** **(13,760,830)**

AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CMR, complete molecular remission (≤MR4.5; *BCR–ABL1*:*ABL1* transcript ratio ≤0.0032%); GI, gastrointestinal; IV, intravenously; MDS, myelodysplastic syndrome; MRD, measurable residual disease; NA, not available; NSCLC, non-small-cell lung cancer; PMF, primary myelofibrosis; PO, per os (by mouth); QD, quaque die (once a day); SC, subcutaneously. [a]Drug cost reductions were calculated based on public listed drug prices during patent protection in Denmark (https://pro.medicin.dk), the UK (www.nice.org.uk), Germany (www.rote-liste.de) and USA (www.drugs.com). Please note that prices negotiated directly between national health-care systems, hospitals and health-care providers, or health-care insurers and the pharmaceutical companies might differ and often are lower than public listed prices.

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