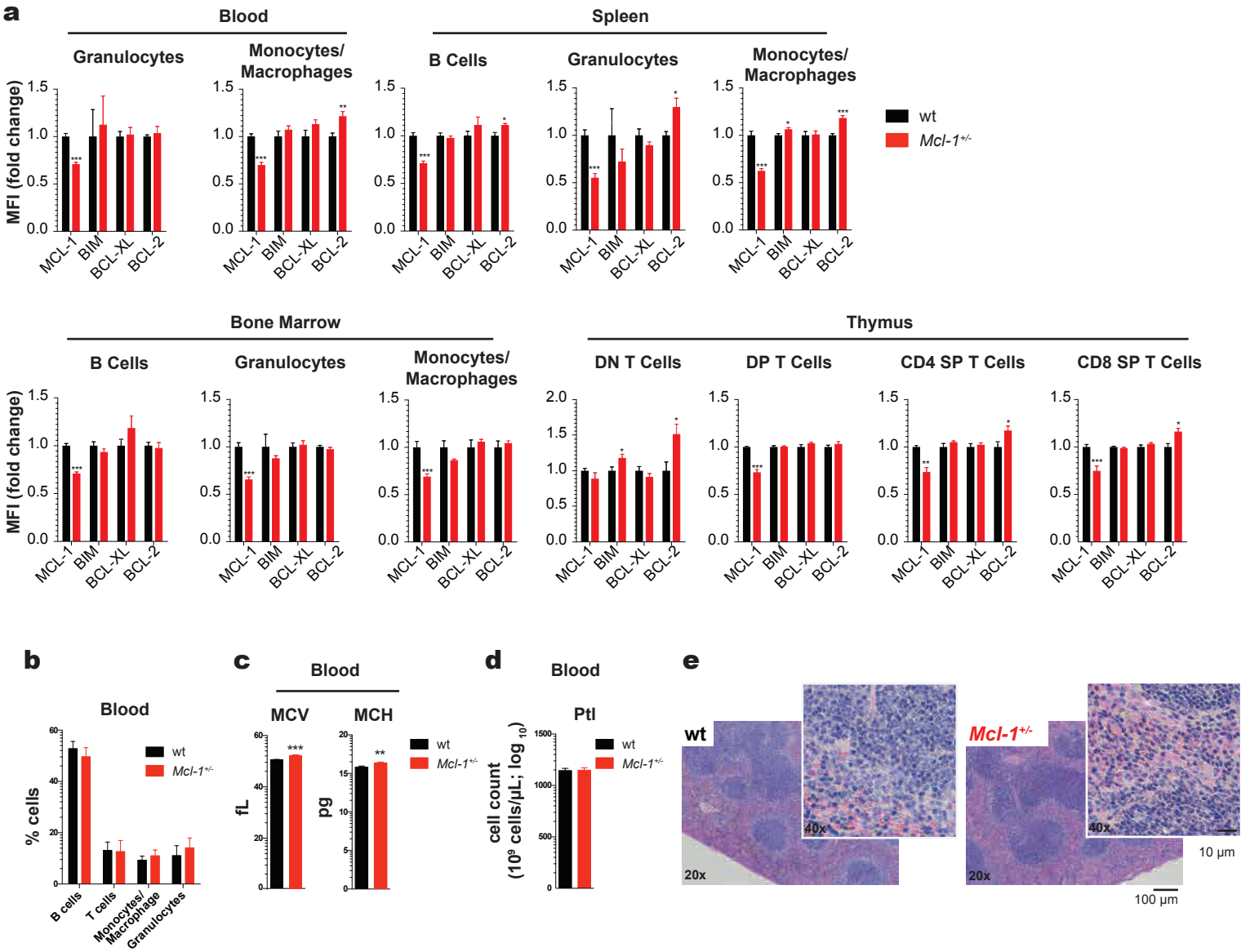
Supplementary Figure S1

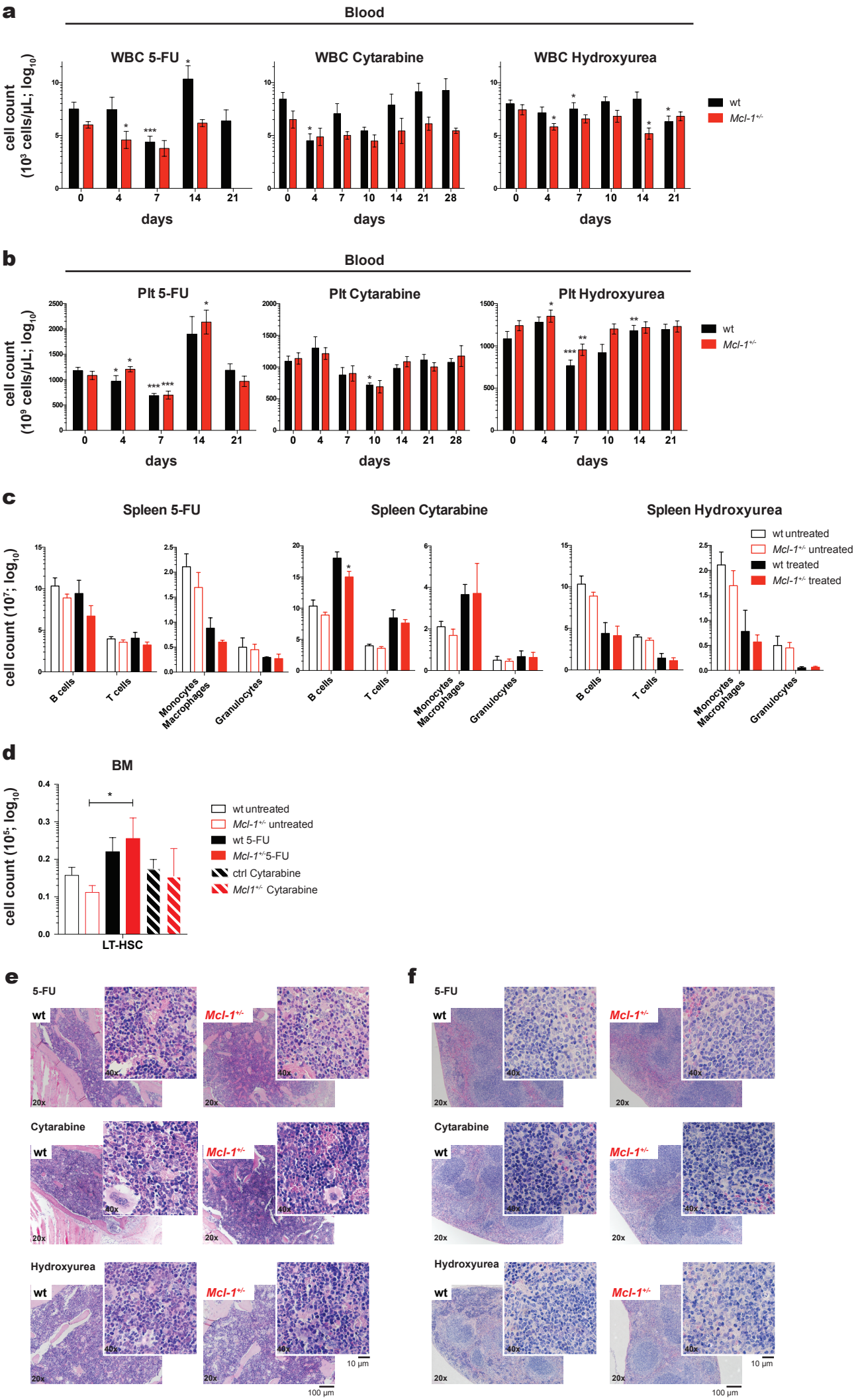


Supplementary Figure S2: Overview of chemotherapeutic drugs and treatment regimes

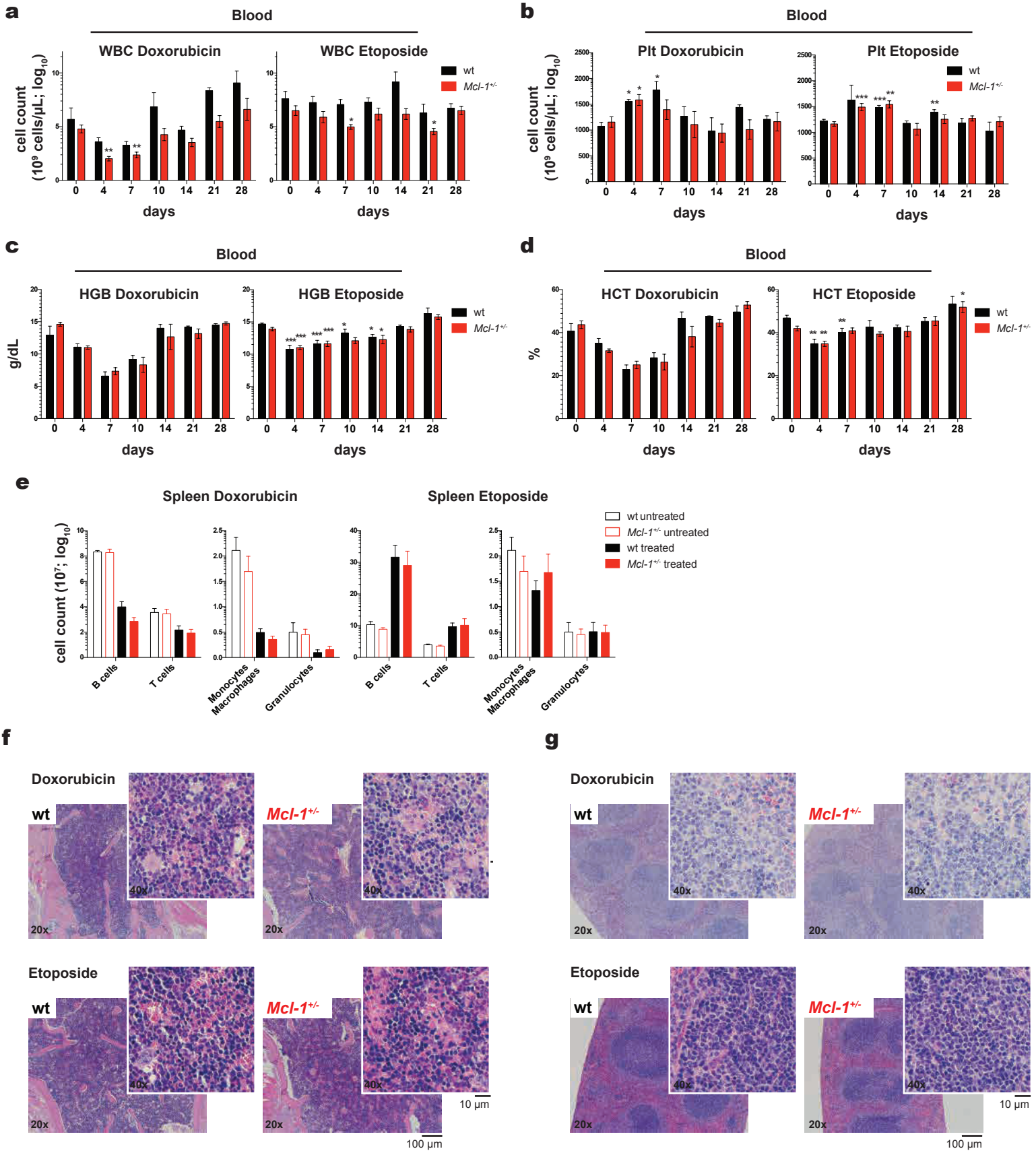
Name	Treatment Protocol	Mechanism of Action	Clinical Relevant Treatment
Fluorouracil (5-FU, Adrucil)	1 x 100 mg/kg body weight, i.v.	inhibits thymidylate synthase and thereby decreases the supply of thymidine	diverse haematological malignancies and several solid cancers (e.g. HL, MM)
Cytarabine (cytosine arabinoside, ara-C)	3 x 80 mg/kg body weight, i.v. (d1, d2, d3)	deoxycytidine triphosphate analog, which is incorporated into DNA during synthesis, causing a stop in DNA replication	AML, ALL, non-HL
Hydroxyurea (Hydroxycarbamide, Hydrea, Litalir, Droxia)	3 x 100 mg/kg body weight, i.p. (d1, d2, d3)	suppresses ribonucleotide reductase, thereby decreasing the production of all deoxyribonucleotides required for DNA synthesis	MDS, CML
Etoposide (Etopophos, Toposar)	1 x 2 mg/kg body weight, i.v.	inhibitor of topoisomerase II, induces DNA double-strand breaks	diverse haematological malignancies and several solid cancers (e.g. HL, MM)
Doxorubicin (Adriamycin, Doxil, Caelyx, Myocet)	2 x 2 mg/kg body weight, i.v. (d1, d2)	DNA intercalating agent, induces DNA double-strand breaks	diverse haematological malignancies and several solid cancers (e.g. HL, MM)
Dexamethasone	3 x 10 mg/kg body weight, i.v. (d1, d2, d3)	steroid medication	diverse haematological malignancies (e.g. MM)
Paclitaxel (Taxol, Abraxene, Onxol)	3 mg/kg body weight, i.v. (d1, d2, d3)	tubulin toxin	AML and several solid cancers

i.v=intravenous, i.p= intraperitoneal, HL=Hodgkin's Lymphoma, MM=Multiple Myeloma, AML=Acute Myeloid Leukaemia, ALL=Acute Lymphoblastic Leukaemia, MDS=Myelodysplastic Syndrome, CML=Chronic Myeloid Leukaemia

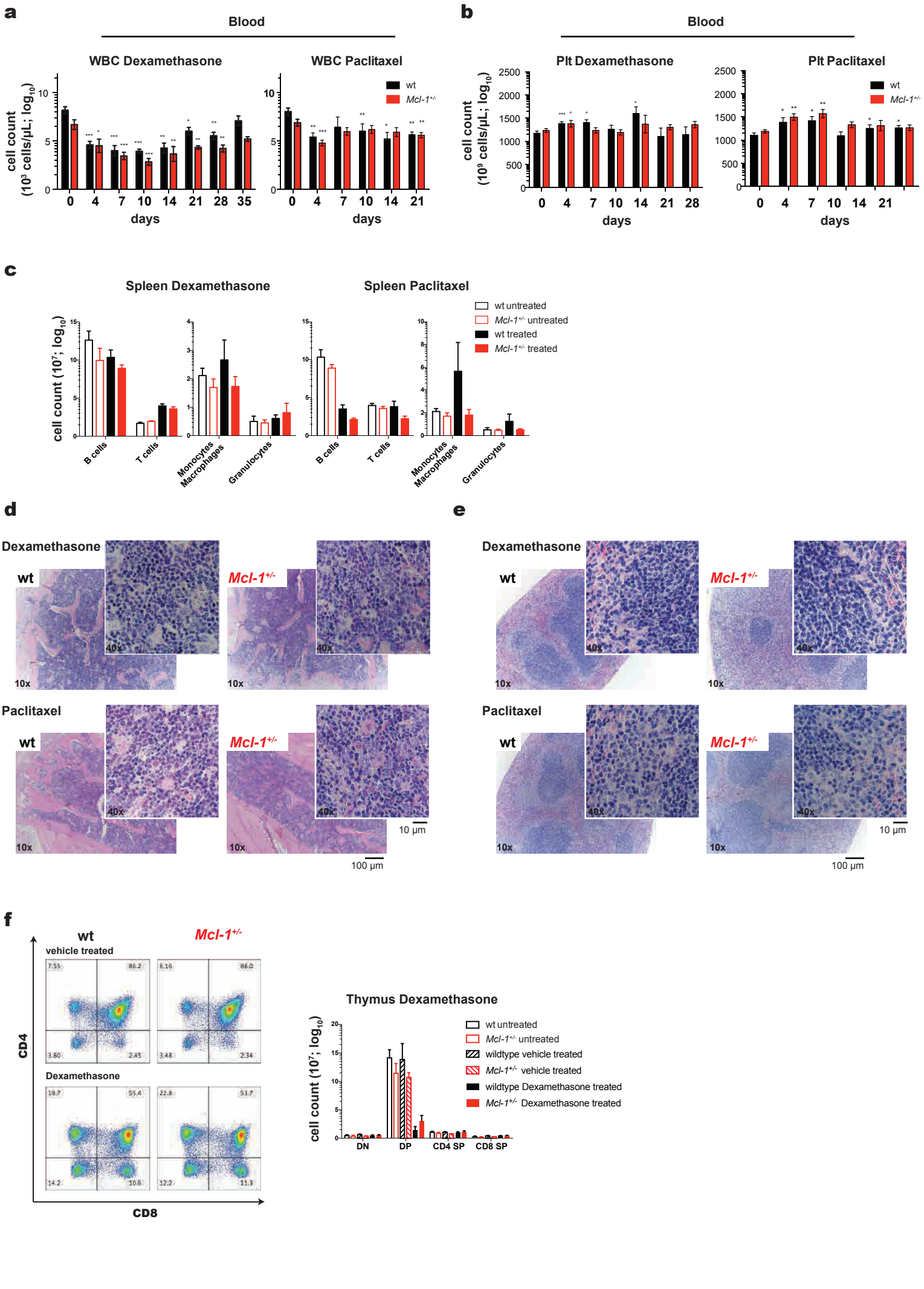
Supplementary Figure S3



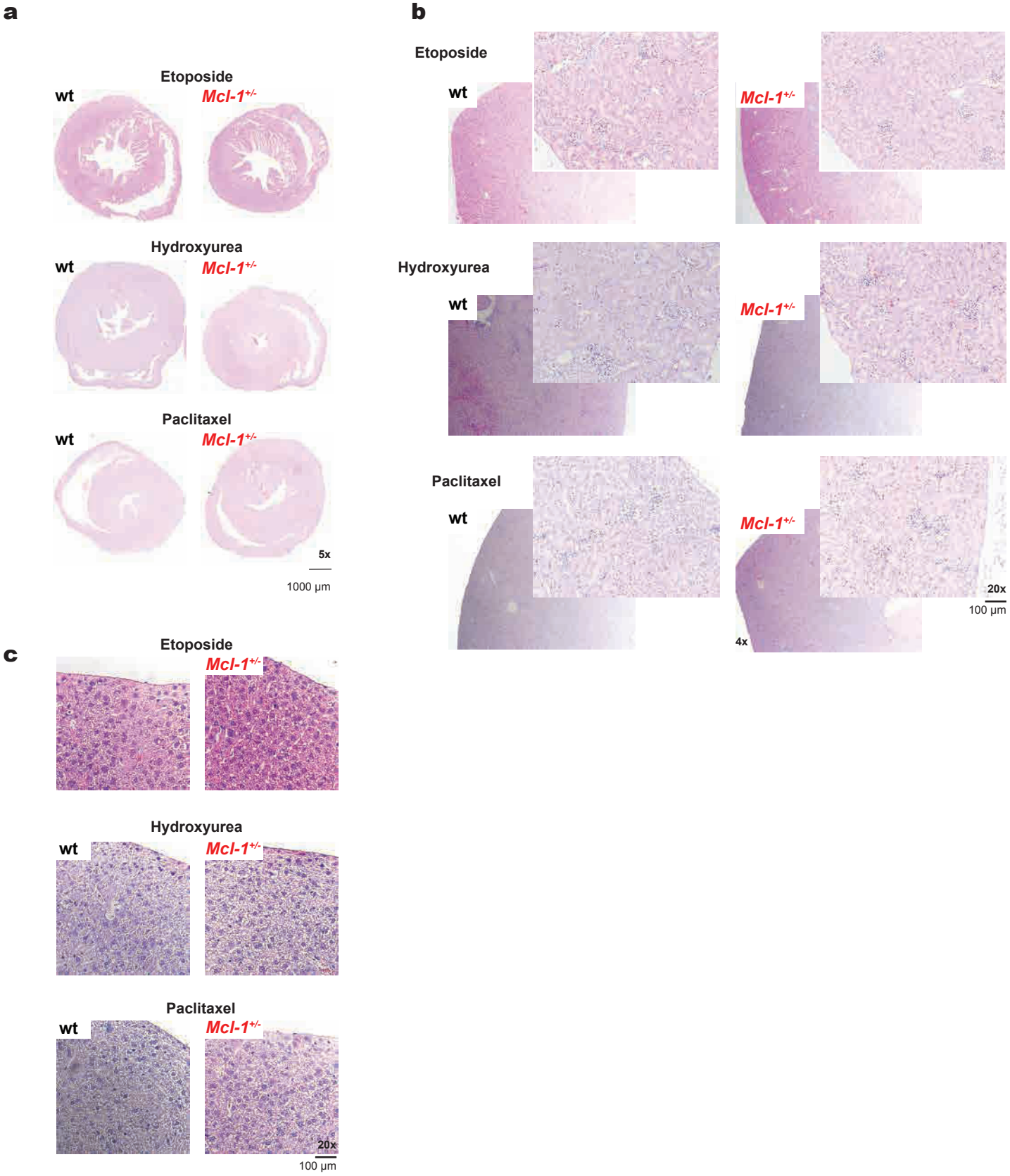
Supplementary Figure S4



Supplementary Figure S5



Supplementary Figure S6:



Supplementary Figure Legends

Supplementary Figure S1

Reduction in MCL-1 levels causes a significant albeit minor reduction in certain blood cell subsets. **(a)** Intracellular FACS staining for MCL-1, BIM, BCL-XL and BCL-2 protein in the indicated cell populations of the blood, spleen, bone marrow and thymus. The different haematopoietic cell subsets were identified by staining with surface marker specific antibodies. Data represent relative mean fluorescence intensity (MFI) ±SEM for cells from wild-type (wt, n≥5) and *Mcl-1*$^{+/-}$ mice (n≥5). *p<0.05, **p<0.01, ***p<0.001 (Student t test, 2 tailed, unpaired, comparing wild-type with *Mcl-1*$^{+/-}$ mice). **(b)** Flow cytometric analysis of the indicated cell populations (%) in the blood of wild-type (n=7) and *Mcl-1*$^{+/-}$ mice (n=7). **(c)** Median corpuscular volume (MCV), median haemoglobin content (MCH) of red blood cells and **(d)** platelet (Ptl) numbers, were determined in the blood of wild-type (n=42) and *Mcl-1*$^{+/-}$ (n=54) mice. Data represent mean ±SEM. *p<0.05, **p<0.01, ***p<0.001 (Student t test, 2 tailed, unpaired). **(e)** Histological analysis of H&E-stained sections of the spleens of wild-type and *Mcl-1*$^{+/-}$ mice.

Supplementary Figure S2

Overview of chemotherapeutic drugs and treatment regimes.

Supplementary Figure S3

Reduction in MCL-1 levels only moderately exacerbates the haematopoietic cytopenia caused by drugs that interfere with DNA synthesis. (a) White blood cell (WBC) and **(b)** platelet (Plt) numbers were determined in wild-type (wt) and *Mcl-1*$^{+/-}$ mice at the indicated time points post-treatment with 5-FU (left panel; wild-type n=8; *Mcl-1*$^{+/-}$ n=8), Cytarabine (middle panel; wild-type n=10; *Mcl-1*$^{+/-}$ n=9) or Hydroxyurea (right panel; wild-type n=12; *Mcl-1*$^{+/-}$ n=11). Data represent mean ±SEM. *p<0.05, **p<0.01, ***p<0.001 (Student t test, 2 tailed, paired, compared to untreated). **(c)** Flow cytometric analysis of total spleen cells in wild-type and *Mcl-1*$^{+/-}$ mice 7 days post-treatment with 5-FU (left panel; wild-type n=3; *Mcl-1*$^{+/-}$ n=3), Cytarabine (middle panel; wild-type n=6; *Mcl-1*$^{+/-}$ n=6) or Hydroxyurea (right panel; wild-type n=3; *Mcl-1*$^{+/-}$ n=3) compared to untreated wild-type (n=7) and *Mcl-1*$^{+/-}$ (n=7) mice. Data represent mean ±SEM. *p<0.05 (Student t test, 2 tailed, unpaired, comparing wild-type with *Mcl-1*$^{+/-}$ mice). **(d)** Flow cytometric analysis of long-term haematopoietic stem

cells (LT-HSC) in the bone marrow (total cell count per one femur) identified by staining with a cocktail of lineage marker specific antibodies and antibodies to detect CD48 and CD150 in wild-type and *Mcl-1*$^{+/-}$ mice 7 days post-treatment with 5-FU (left panel; wild-type n=5; *Mcl-1*$^{+/-}$ n=5) or Cytarabine (right panel; wild-type n=3; *Mcl-1*$^{+/-}$ n=3) compared to untreated wild-type (n=5) and *Mcl-1*$^{+/-}$ (n=5) mice. Data represent mean ±SEM. *p<0.05, (Student t test, 2 tailed, unpaired, comparing the indicated groups). Histological analysis of H&E-stained sections of the bone marrow (sternum) **(e)** and spleen **(f)** of wild-type and *Mcl-1*$^{+/-}$ mice treated with 5-FU (21 days post-treatment, upper panel), Cytarabine (28 days post-treatment, middle panel) or Hydroxyurea (21 days post-treatment, lower panel).

Supplementary Figure S4

Reduction in MCL-1 levels only moderately exacerbates haematopoietic cytopenia caused by DNA double strand break-inducing drugs. (a) White blood cell (WBC) numbers**, (b)** platelet (Plt) numbers, **(c)** haemoglobin (HCT) content and **(d)** haematocrit (HGB) were determined in wild-type (wt) and *Mcl-1*$^{+/-}$ mice at the indicated time points post-treatment with Doxorubicin (wild-type n=9; *Mcl-1*$^{+/-}$ n=8) (left panel) or Etoposide

(wild-type n=8; *Mcl-1*$^{+/-}$ n=8) (right panel). Data represent mean ±SEM. *p<0.05, **p<0.01, ***p<0.001 (Student t test, 2 tailed, paired, compared to untreated). **(e)** Flow cytometric analysis of total spleen cells in wild-type and *Mcl-1*$^{+/-}$ mice 7 days post-treatment with Doxorubicin (left panel, wild-type n=3: *Mcl-1*$^{+/-}$ n=3) or Etoposide (right panel, wild-type n=3: *Mcl-1*$^{+/-}$ n=3) compared to untreated wild-type (n=7) and *Mcl-1*$^{+/-}$ mice (n=7). Data represent mean ±SEM. p>0.5 (n.s.) (Student t test, 2 tailed, unpaired, comparing wild-type with *Mcl-1*$^{+/-}$ mice). Histological analysis of H&E-stained sections of the bone marrow (sternum) **(f)** and spleen **(g)** of wild-type and *Mcl-1*$^{+/-}$ mice 28 days post-treatment with Doxorubicin (upper panel) or Etoposide (lower panel).

Supplementary Figure S5

Reduction in MCL-1 levels does not drastically exacerbate haematopoietic cytopenia caused by non-DNA-damaging chemotherapeutic drugs. White blood cell (WBC) **(a)** and platelet (Plt) **(b)** numbers were determined in wild-type (wt) and *Mcl-1*$^{+/-}$ mice at the indicated time points post-treatment with Dexamethasone (left panel) or Paclitaxel (right panel). Data represent mean ±SEM. *p<0.05, **p<0.01, ***p<0.001 (Student t test, 2-tailed, paired, compared to

untreated mice). **(c)** Flow cytometric analysis of total spleen cells in wild-type and *Mcl-1*$^{+/-}$ mice 7 days post-treatment with Dexamethasone (left panel; wild-type n=3: *Mcl-1*$^{+/-}$ n=3) or Paclitaxel (right panel, wild-type n=3: *Mcl-1*$^{+/}$ n=3) compared to untreated wild-type (n=7) and *Mcl-1*$^{+/-}$ mice (n=7). Data represent mean ±SEM. p>0.5 (n.s.) (Student t test, 2 tailed, unpaired, comparing wild-type with *Mcl-1*$^{+/-}$ mice). Histological analysis of H&E-stained sections of the bone marrow (sternum) **(d)** and the spleen **(e)** of wild-type and *Mcl-1*$^{+/-}$ mice treated with Dexamethasone (35 days post-treatment, upper panel) or Paclitaxel (21 days post-treatment, lower panel), respectively. **(f)** Representative examples of flow cytometric analysis of thymic T lymphoid cell populations identified by staining for CD4 and CD8 (left panel). Data are presented as mean ±SEM of total numbers of the indicated cell subsets in the thymi from wild-type (untreated: n=7, vehicle: n=2, Dexamethasone: n=3) and *Mcl-1*$^{+/-}$ (untreated: n=7, vehicle: n=2, Dexamethasone: n=3) mice (right panel). p>0.5 (n.s.) (Student t test, 2 tailed, unpaired, comparing wild-type with *Mcl-1*$^{+/-}$ mice). DN=double negative; DP=double positive; SP single positive thymocytes.

Supplementary Figure S6

Reduction in MCL-1 levels does not cause cardio-, nephro- or hepato-toxicity. Histological analysis of H&E-stained sections of the **(a)** heart**, (b)** kidney and **(c)** liver of wild-type and *Mcl-1*$^{+/-}$ mice treated with Etoposide (28 days post-treatment, upper panel), Hydroxyurea (21 days post-treatment, middle panel), or Paclitaxel (21 days post-treatment, lower panel).