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Commentary regarding distribution and pharmacokinetics of melflufen in humans

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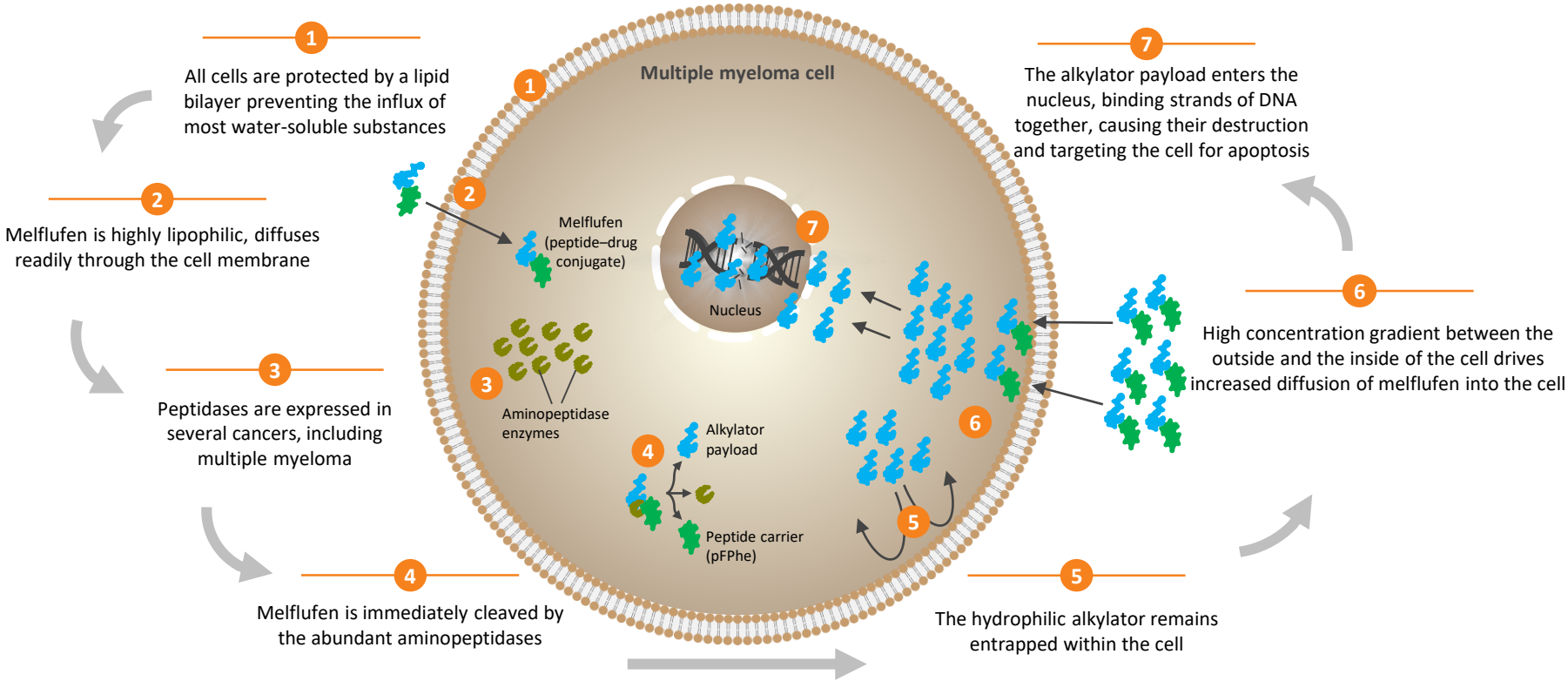
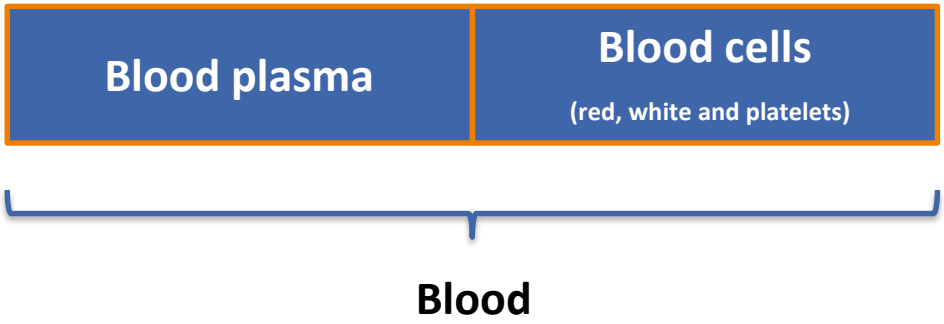
Melflufen is a novel peptide-drug conjugate

- Uses high peptidase levels to target myeloma cells



Chauhan D, et al. Clin Cancer Res 2013;19(11):3019-3031; Wickström M, et al. Invest New Drugs 2008;26(3):195-204; Ray A, et al. Br J Haematol 2016;174(3):397-409; 4. Strese S, et al. Biochem Pharmacol 2013;86(7):888-895; Wickström M, et al. Oncotarget 2017; 8(39):66641-66655.

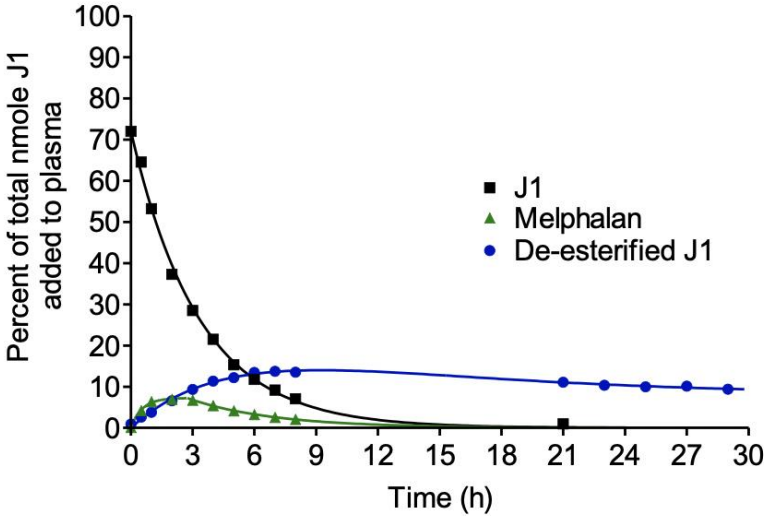
During infusion melflufen ends up in the blood plasma



- Melflufen is given intravenously over 30 minutes
- This means that the drug ends up in the plasma of the blood in the patient during infusion

Melflufen is not degraded in human plasma

Melflufen in human plasma (no cells present)



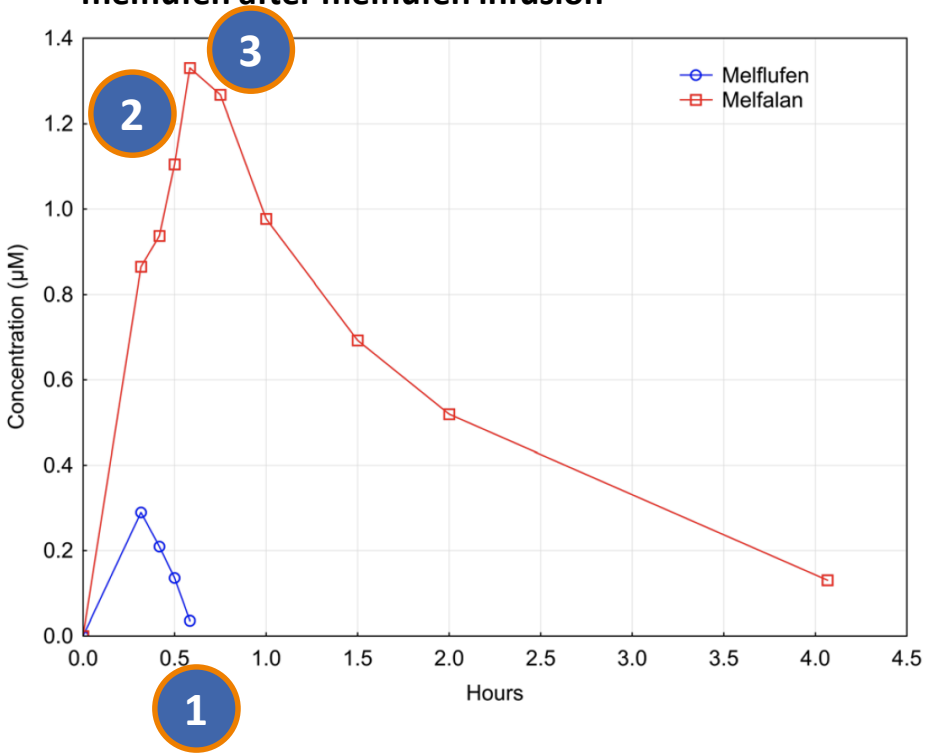
- **J1 = melflufen (J1 is the old experimental drug name)**
- **In human plasma it takes roughly 12 hours for all melflufen to disappear**
- **Since aminopeptidase degradation of melflufen into melphalan is very rapid the conclusion is that aminopeptidase activity in human plasma is negligible**
- **The technical half life in human plasma is 2.3 hours**

Conclusion: There is no relevant aminopeptidase activity in human plasma

Source: Nygren 2009

Pharmacokinetic characteristics of melflufen – patient example – 30 minute infusion

Concentration in plasma of melphalan and melflufen after melflufen infusion



- **Only a small amount of infused melflufen is ever measurable**
- **After the end of infusion, melflufen disappears within seconds from the plasma (1)**
- **Melphalan concentration continuous to increase after melflufen has disappeared from the plasma (2)**
- **Peak concentration of melphalan in plasma is significantly lower after infusion of melflufen than after an equivalent dose of melphalan itself (3)**

Source: Berglund 2015

Observations so far

- Melflufen is infused intravenously to the plasma compartment of the patient and then rapidly disappears (seconds-minute time-frame)
- However, human plasma does not degrade melflufen
- Consequently, the conclusion is that melflufen is rapidly taken up by cells after infusion
- Furthermore, since we cannot measure melflufen quickly after the end of infusion - but we can measure melphalan - we know that close to 100% of melflufen is cleaved by intra-cellular aminopeptidases
- Question: Where does melflufen end up?

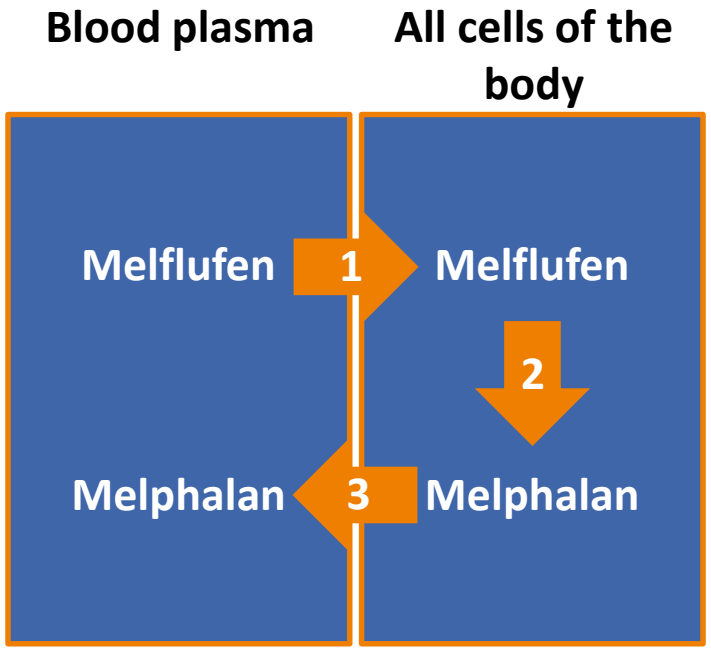
Conclusion: Melflufen is rapidly taken up by cells after infusion and cleaved by intra-cellular aminopeptidases

Principles of diffusion and relevance for melflufen

- Diffusion is the law that all concentrations become equal across a medium over time. This is driven by the 2nd law of thermodynamics
- Diffusion over millimeter/centimeter distances takes minutes to hours (to equalize concentrations)
- This is the reason why evolution has given us capillary beds – by compressing distances between the plasma, blood cells and cells in organs to micrometer distances, diffusion happens within milliseconds
- Normally in then body, cell membranes act as barriers for molecules. However, this does not work with lipophilic substances (fat soluble) such as anesthetic compounds since they want to enter cell membranes
- Melflufen is as lipophilic as anesthetic compounds (logP of around 4) and is consequently equalized over the capillary bed between the blood and the cells of various organs. The only limitation is blood flow.

Conclusion: Melflufen is evenly distributed between all cells of the body as a function of blood flow

Graphical overview



1. Melflufen is evenly distributed to all cells of the body through diffusion over the capillary beds
2. Degradation of melflufen into melphalan is done by aminopeptidases inside cells (close to zero blood plasma activity)
3. Melphalan is redistributed from inside the cells to the blood plasma in accordance to the laws of diffusion since no melphalan is formed in the blood plasma

Summary

- Melflufen is infused intravenously to the plasma compartment of the patient and then rapidly disappears (seconds-minute time-frame)
- However, human plasma does not degrade melflufen
- Due its lipophilicity, melflufen is evenly distributed to all cells of the body over the capillary bed in accordance to the laws of diffusion
- Inside the cells (intra-cellularly) aminopeptidases cleave melflufen to release melphalan
- Since no melphalan is formed in the plasma the same laws of diffusion then ensures that melphalan is slowly released to the plasma from the intra-cellular compartments

Thank you!

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