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Quality of Gemcitabine ready to administer preparations

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Introduction

Gemcitabine ready to administer (RTA) bags are frequently prepared in hospital pharmacies. Long term stability for 84 days has been demonstrated [1] and dosebanding for this substance is already established at some hospitals. Dosebanding has the advantage of quality control before use. However, with increasing storage time bags may loose quality due to degradation products with unknown effects. Little is known about the quality of different gemcitabine RTA preparations.

Materials and Methods

We prepared 10mg/ml Gemcitabine infusion bags and compared content, degradation products and pH with an industrial RTA bag with same concentration. We stored the bags at 22°C and used a stability indicating HPLC/DAD and LC-MS method with an ReproSIL-Pur Basic C18 column (Eluent isocratic mixture of 97% formic acid 0,1% and 3% methanol). The method follows the guidelines for the practical stability studies of anticancer drugs [2].

Results

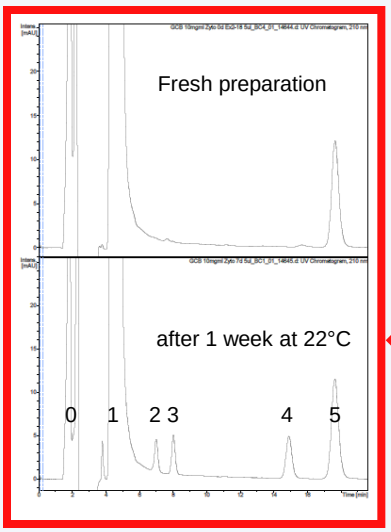

Fig. 1: Chromatograms of the Gemcitabine bag prepared in the pharmacy lab from a concentrate (Manufacturer A)

physiological pH
Stability 2 years
less degradation
pH 7

pH 3
unphysiological pH
Stability 84 days
more degradation

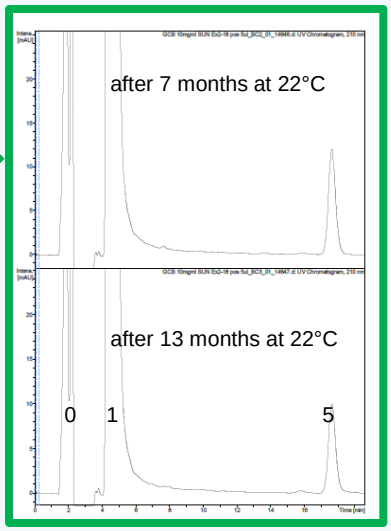

Fig. 2: Chromatograms of the Gemcitabine RTA bag (Manufacturer B)

0 = Injection Peak
1= Gemcitabine
2= diastomeric alcohol $C_9H_{12}N_2O_6F_2$
3= diastomeric alcohol $C_9H_{12}N_2O_6F_2$
4 = O6,5'-Cyclo-5,6-dihydro-2'-desoxy-2',2'-difluoruridin
5= 2'-Desoxy-2',2'-difluoruridin (dFdU)

We could confirm stability for 84 days in all gemcitabine preparations with 0,9%NaCl, while the Gemcitabine concentration always exceeded 95%. The content of all tested degradation products was significantly higher in the bags produced in pharmacy lab (Fig.1). In these bags the content of four degradation products increased significantly during storage time, whereas in the industrial RTA bag only a small amount of dFdU was found (Fig.2). The signal of dFdU did not increase during a storage time over 13 month. The pH was about 7.0 whereas the pH in the bags diluted from gemcitabine concentrate was initially 2.7 and 2,6 after 84days storage at 22°C.

Conclusions

We conclude that Gemcitabine preparations adjusted to neutral pH have a longer apparent stability with less degradation products during storage. The advantages are longer stability with no increase of hydrolysis products over storage and the physiological pH may be more comfortable for the patient. To improve quality, changing the pH in gemcitabine preparations should be considered.

References:
[1] H. Reinhardt , R. Trittler, A.G. Eggleton, S. Wöhrl, T. Epting, M. Buck, S. Kaiser, D. Jonas, J. Duyster, M. Jung, M.J. Hug, M. Engelhardt. Paving the Way for Dose Banding of Chemotherapy: An Analytical Approach J Natl Compr Canc Netw 2017;15(4):484–493
[2] C. Bardin, A. Astier, A. Vulto, G. Sewell, J. Vigneron, R.Trittler, M. Daouphars, M. Paul, M. Trojniak, F. Pinguet. Guidelines for the practical stability studies of anticancer drugs: A European consensus conference. Annales Pharmaceutiques Francaise 2011; 69: 221-231

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