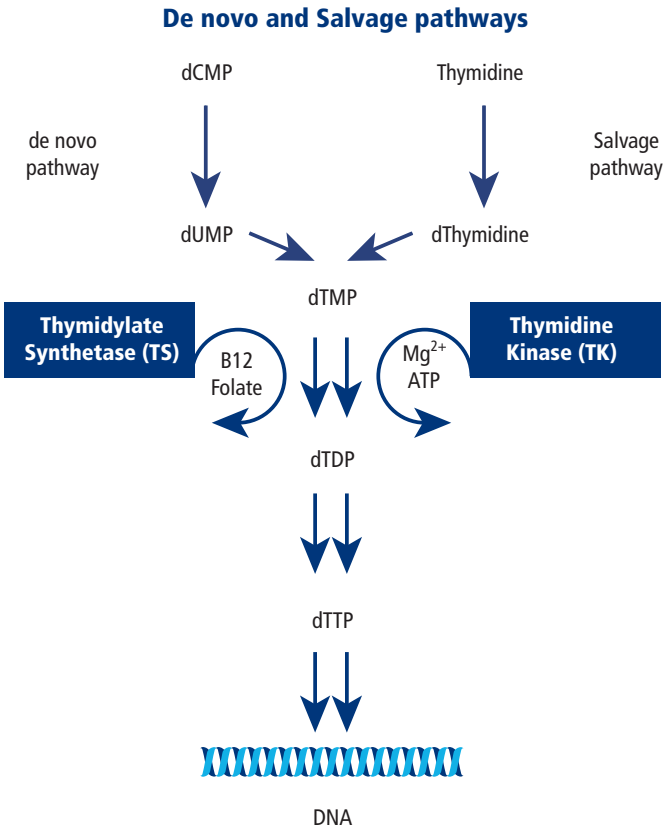
Thymidine Kinase (TK)

Thymidine Kinase reflects proliferative activity of the tumour

Thymidine Kinase is a cytosolic enzyme known to be involved in DNA synthesis [1]. DNA is synthesized following one of two possible pathways **(Fig. 1):** the de novo pathway or the Salvage pathway. In the latter thymidine kinase catalyzes conversion of deoxythymidine to deoxythymidine monophosphate. Subsequent steps lead to DNA-synthesis as shown in Figure 1. The pathway catalyzed by TK is called the Salvage pathway since it uses either exogenous or endogenous deoxythymidine.

Fig. 1



Mammalian cells contain two different Thymidine Kinase isoenzymes[2], cytosolic Thymidine Kinase 1 (TK1) and mitochondrial Thymidine Kinase 2 (TK2). TK1 is associated with cell proliferation whereas TK2 is needed for mitochondrial DNA synthesis. TK1 activity increases markedly in the G1/S phase of the cell cycle. TK1 has therefore been shown to be a reliable marker of cell proliferation – the only proliferation marker that can be measured in serum (S-TK) [3].

TK in Haematological Malignancies

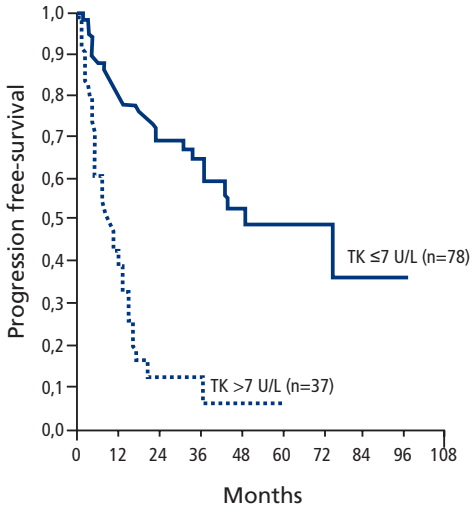
Non-Hodgkin's Lymphoma (NHL)

Several studies have shown the value of S-TK as a prognostic marker [5]. Pretreatment levels have been found to be a powerful discriminator of disease stage and to provide prognostic information. S-TK levels are able to predict response to treatment and survival. S-TK values seem also to be higher in high-grade NHL than on low-grade NHL [6-9]. Furthermore S-TK levels are useful in predicting the disease course in low-grade NHL. S-TK values are found to return to normal if the treatment is successful. A renewed increase indicates recurrence and/or transformation into a more malignant form of the disease [10].

Chronic Lymphocytic Leukaemia (CLL)

The current staging systems in CLL such as Binet or Rai classification do not accurately predict the individual risk of disease progression. The S-TK levels in patients with CLL have been shown to have a remarkably prognostic capability. Patients with a serum level above 7.1 U/L have an average time of Progression-Free Survival of about 8 months, whereas patients with levels below this concentration have a Progression-Free Survival of almost 49 months, which is similar to that of patients with smouldering CLL **(Fig. 2)**[8,11].

Fig. 2



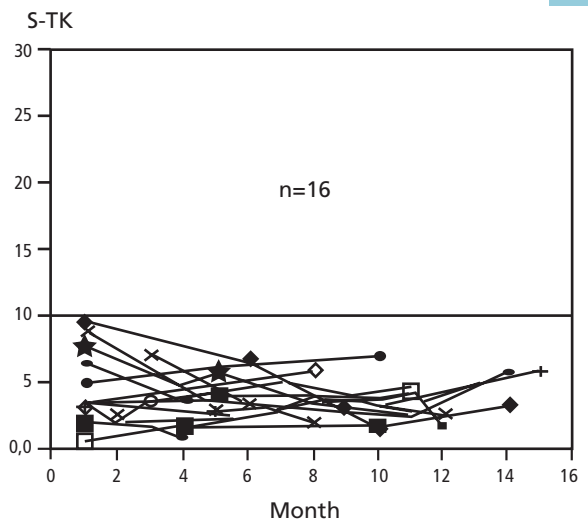
Progression-Free Survival of Binet stage A patients in relation to high versus low serum TK level. The cut-off used was 7.1 U/L

Hallek et al. [8]

Multiple Myeloma (MM)

It has been shown that S-TK levels correlate with clinical stage and survival time. Furthermore S-TK levels have been found to be useful in distinguishing between MM and monoclonal gammapathy of undetermined significance (MGUS) **(Fig. 3)**[12,13].

Fig. 3a



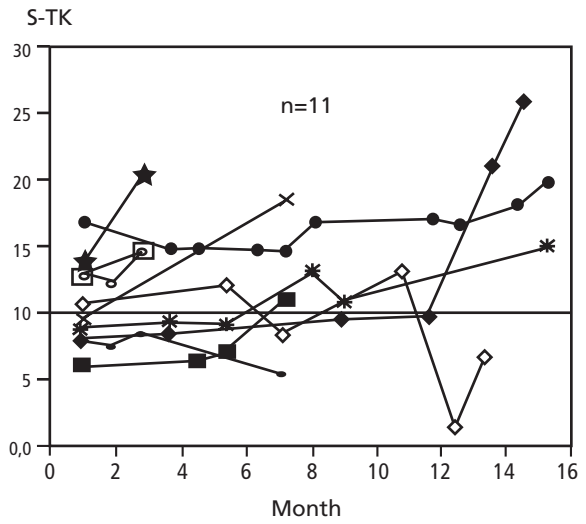
Follow-up of MM patients with smouldering myeloma

Poley et al. [12]

Hodgkin's lymphoma

Significant correlations have been found between S-TK levels and the stage of the disease. When the prognostic ability was examined, patients in stages IA and IIA could be divided according to S-TK levels into two different groups in relation to Disease-Free Survival. This finding makes S-TK interesting as an additional tool in clinical evaluation and in the therapeutic decision concerning patients with Hodgkin's disease [14].

Fig. 3b



Follow-up of MM patients with active disease

Poley et al. [12]

Acute Myeloic Leukaemia (AML) and Acute Lymphocytic Leukaemia (ALL)

S-TK determinations detect recurrent disease at an early stage, before it can be detected microscopically. There is a close correlation between S-TK levels and the count of leukocytes, the percentage of blasts in the blood, the therapeutic response and the length of survival after the initial diagnosis. Therefore S-TK levels indicate the aggressiveness of leukaemic cells and predict the response to the treatment and the length of survival [15-17].

MyeloDysplastic Syndrome (MDS)

High S-TK in MDS predicts transformation of MDS to Acute Myeloid Leukaemia. Multivariate analysis confirmed the independent prognostic value of S-TK for both overall survival and risk of acute transformation. We conclude that S-TK may be an important prognostic factor in MDS, which is strongly correlated to development of AML.

Conclusions

- S-TK has proven to be a reliable marker of tumour cell proliferation
- S-TK provides a valuable tool to assess disease activity in untreated haematological malignancies and for monitoring of treatment, remission and smouldering disease
- S-TK predicts clinical relapse months before the onset of clinical symptoms