INTRODUCTION: Mathematical models describing the tumor growth in animals often neglect the relationship between tumor and host organism. To overcome this limitation, a mechanistic PK/PD model combining the Dynamic Energy Budget (DEB) theory [2] with the Simeoni Tumor Growth Inhibition (TGI) model [3] and describing both the dynamics of the tumor-host interaction and the effect of anticancer treatments was developed [1].

OBJECTIVES: A new identification strategy for a slightly revised model formulation has been tested on data collected during 9 different experiments involving six novel anticancer candidates and six drugs already available on the market. Moreover, the tumor growth in control groups has been compared between the DEB-TGI model and the widely used Simeoni TGI model.

METHODS:

Datasets: Data for model validation refer to xenograft experiments conducted on Harlan Sprague Dawley mice. In these experiments the tumor and the net body weight of control and treated animals were collected at different doses; average data were considered. The PKs were derived from separate studies. The reported example involves male mice treated with vehicle (arm a) and three groups treated with drug A following different schedules and doses (arms b, c and d).

The model: e: reserve amount V: organism structural volume

\[ V_{t+1} \text{ tumor volume of proliferating cells} \]
\[ V_{u_2}, V_{u_3}, V_{u_4} \text{ tumor volume of non-proliferating cells in the mortality chain} \]

RESULTS

Identification strategy: Mice growth curve Tumor growth curve

Comparative study: DEB-TGI and Simeoni TGI model:

A dynamic system analysis showed that, as the Simeoni model, the DEB-TGI model predicts an exponential growth of the tumor in the early phases of its development.

The parameter combination describing the exponential growth rate is independent of the structural biomass and the energy reserve and shows that both tumor characteristics and host conditions lead the tumor growth.

\[
\mathbf{A}_0 = \frac{m_{i+1}}{m_i} \mathbf{g}_{u_1} - \mathbf{g}_{u_2}
\]

Tumor weights for 9 datasets were simulated by using estimates obtained from the DEB-TGI model identification on the control groups. Then, the Simeoni model was identified on the simulated datasets.

The two exponential growth rates have always comparable values.

CONCLUSIONS: The tumor-in-host DEB-based model confirmed its good capability in describing tumor and host body growth even when an anticancer drug is administered; it also provides a quantitative measurement of the drug potency \( (K_2) \) and of the drug side effect \( (C_{50}) \). Moreover, from the comparative analysis a physiological meaning has been given to the transition from the exponential to the linear phase for a specific threshold weight of tumor cells, enforcing the robustness and the validity of the Simeoni TGI empirical function.

REFERENCES: