Since the seminal work of Otto Warburg (Warburg 1956), it is known that cancer cells are characterized by an increased uptake of glucose and an elevated secretion of lactic acid accompanied by a significant decrease of involvement of the tricarboxylic acid (TCA or Krebs) cycle (frequently called the Warburg effect). Although hypoxia could cause this altered metabolism, many types of cancer cells metabolize glucose directly to lactic acid even under normoxic conditions, hence the term aerobic glycolysis. There is general agreement that this metabolic alteration provides a proliferative advantage to the cancer cell resulting from a redirection of glucose metabolism that allows the cancer cell to maximize the synthesis of key biomolecules, such as nucleic acids and lipids. There is also a prevailing opinion that the redirection of glucose metabolism is under the control of a variety of oncogetic proteins, such as Akt, c-Myc, and Ras.

Among the numerous changes involved in aerobic glycolysis in cancer cells some are particularly important, for instance: increased uptake of glucose in particular by increased levels of glucose transporter-1, utilization of hexokinase-II as the principle isomerase, reduction of pyruvate kinase activity, inactivation of pyruvate dehydrogenase, and upregulation of ATP citrate lyase. Our hypothesis was that targeting two of more of these specific alterations could be an efficient strategy to inhibit cancer growth.

We initially decided to target both pyruvate dehydrogenase and ATP citrate lyase, encouraged by the recent results of Bonnet et al. (2007) and Hatzivassiliou et al. (2005). We chose to target the inhibition of PDH activity through the use of alpha lipoic acid (ALA), a known inhibitor of PDHI, which is in turn an inhibitor of PDH (Korotchkina et al. 2004), and to inhibit ATP citrate lyase by using a known inhibitor, calcium hydroxycitrate (HCA) (Berkhout et al. 1990).

In a first series of experiments, we reported that these two non-toxic and easily available drugs were highly effective in mouse cancer models when used in combination (Schwartz et al. 2010). The efficacy of this combination appeared to be similar to conventional chemotherapy (cisplatin or 5-FU).

In the present work, our aim was to determine if the use of this combination would be even more effective in combination with classical chemotherapy protocols.

- We studied the efficacy of this combination of drugs as an add-on therapy to cisplatin in two different models.
- To generalize our findings, we determined if the combination of lipoic acid and hydroxycitrate could also be effectively combined with another chemotherapeutic drug, such as methotrexate.

Aims

Results

Background

Figure 1: ALA+HCA is equivalent to CIS whereas ALA+HCA+CIS is more efficient than CIS against the lung carcinoma (LL/2) cancer model.

Materials & Methods

Conclusions

References


Figure 2: ALA+HCA is equivalent to CIS whereas ALA+HCA+CIS tends to be more effective than CIS against the bladder transitional cell (MBT-2) cancer model.

- Chemicals: lipoic acid, cisplatin and methotrexate were purchased from Sigma and calcium hydroxycitrate (Garcinia cambogia extract containing 60% hydroxycitrate plus calcium-potassium salt) from Indo World Trading Corporation (New Delhi, India). The following dosages were used: lipoic acid (110 mg/kg, twice a day), calcium hydroxycitrate (250 mg/kg, twice a day), cisplatin (1 mg/kg every other day) and methotrexate (1 mg/kg/day). All drugs were diluted in saline solution (0.9% NaCl) for administration.

- Tumor models: C3H (6 weeks old) and C57BL/6 mice (8 weeks old) were used depending on the cell lines.

- For the lung carcinoma cancer model, we implanted 10² L2/2 cells subcutaneously in the back of C57BL/6 mice (n=9/group). After randomization (mean tumor volume: 102.0mm³), treatments were administered intraperitoneally for 21 days. Mice were treated either by drug alone or by a combination of two or three molecules.

- For the bladder cancer model, we implanted 10² MBT-2 cells subcutaneously in the back of C3H mice (n=9/group). After randomization (mean tumor volume: 93.4mm³), treatments were administered intraperitoneally for 21 days. Mice were treated by calcium hydroxycitrate and lipoic acid or cisplatin, or the combination of the three drugs.

- Tumor response: animal weight and tumor size were measured twice a week. Tumour volume in mm³ was calculated from the measurement of two perpendicular diameters using a calliper according to the formula l x l x h x π/6, where l and h are the largest and smallest diameters and h the height in mm, respectively (Tomoyko and Reynolds 1989).

Figure 3: ALA+HCA+MTX treatment is more effective than MTX against the lung carcinoma (LL/2) cancer model.

- The combination of alpha lipoic acid (pyruvate dehydrogenase activator) and calcium hydroxycitrate (ATP citrate lyase inhibitor) inhibits tumor growth in LLC and MBT-2 mouse cancer models.

- The ALA+HCA combination potentiates the effectiveness of standard chemotherapeutic drugs such as cisplatin and methotrexate.