Rethink the war on cancer – Directional metastasis driven by survival advantage gradient

The overall strategy of fighting cancer has not changed since 1971 when President Nixon declared a war on cancer: That is to kill them head-to-head with all types of weapons we have developed including surgical removal, chemo-, radio- and, more recently, molecular targeted and anti-angiogenesis therapies or combinations thereof. Certainly we have won some battles (e.g. pediatric leukemia) but many more to be seen on the side of “Lost” list, especially on the adult cancers. The fact that the overall cancer death rate (around 200 deaths in 100,000 population) has not really changed over the past 50 years [1] has suggested we are not on the winning track. In a real war, if we are not winning with the current strategy, it will be a logical response to try a different one, so why not in the war with cancer? About 90% of cancer death is caused by metastasis. If we can find some way to control metastasis, the disease is likely to be controlled. We may not be able to prevent it from happening but can we control its location? If metastasis occurred randomly, we would see them everywhere through the body with equal probabilities. However, this is not what has happened. The most common metastatic sites are lung, bones and liver. Metastatic cells seem to settle in the well-perfused locations with compatible cell–cell adhesion molecules such as E-cadherin, integrins etc. [2]. It has been reported that chemokine receptors CXCR4 and CCR7 are highly expressed in breast cancer cells and their ligands are highly expressed in organs representing initial location of metastasis [3]. Other studies have shown the niche microenvironment may be critical for maintaining the cancer stem cells and the overall cancer cell population [4,5]. The next question is how we use this knowledge. Conventionally, we would try to inhibit those over-expressed “bad guys” and neutralize whatever seems preferred by the cancer cells. I propose a strategy of “Directional Metastasis”, which is to build a safe house somewhere in the body with “friendly” molecules to attract metastatic cells. Take the breast cancer for instance, we can fill the “safe house” with ligands for CXCR4 and CCR7 and construct a microenvironment that is preferred by the metastatic breast cancer cells. Consequently, the safe house would appear to metastatic cells that we are working with them instead of against them. If the “safe house” strategy is combined with conventional killing strategy, which puts a huge survival pressure on metastatic cancer cells, we may be able to create a survival advantage gradient that drives the metastatic cells to migrate to the safe house.

Since the nature of this strategy is not to “harm”, the risk associated with toxicity is expected to be minimized. A foreseeable risk is it may not work the way we expect. For example, even when the metastatic cells are attracted to the “safe house”, they may still escape unless a localized treatment can be delivered before they do. The ad hoc risk and feasibility should be assessed on an approach where specific hypotheses can be proposed. If the strategy works, metastasis will be directed in a location we designate instead of places they choose. Therefore, the treatment can be focused on the primary site and the “safe house(s)”. It then may be possible to reduce the systemic treatment and use more localized treatment to reduce global toxicity. It may not eventually work out the way I propose here. But once we start to explore this strategy, ground-breaking approaches may be developed. We have been sticking cancer long enough; maybe it’s time to give a carrot.

References


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Stone gum: To prevent the stone migration and provide stone clearance during percutaneous nephrolithotomy

With the technological advancements in endoscopes and endolithotripters, the percutaneous nephrolithotomy (PNL) is regarded as the first treatment choice in large renal stones. Despite to all improvements in technique, the success rate of the PNL ranges from 40% to 90% [1]. And incontrovertible rates (70%) of the patients are left with residual stone fragments after the procedure [2]. These residual fragments may lead to stone related event and further intervention such as second look flexible nephroscopy, extracorporeal shock wave lithotripsy or ureteroscopy after the initial procedure and additional expense and morbidity to the patient.

Small stone fragments are generally migrated to the other calices during the stone disintegration [3]. The usage of pneumatic lithotripter in single pulse mode or flushing out the collecting system may reduce the residual fragment left in kidney [4]. Despite to all efforts the scattering of the stone fragments is not prevented. Although ureteral occlusion devices are used to prevent the stone
migration to the proximally during the endoscopic treatment of the ureteral stones, no instrument is improved for the PNL procedure [5].

During the PNL it is observed that the blood clots are adhered to the stone fragments and so that scattering of the small fragments is prevented. By the removal of these clots, the stone clearance is provided. We hypothesize that a stone gum acting like a fishing net may prevent the scattering of the stone fragments and may improve stone free status of the PNL procedure.

References


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Increased endogenous erythropoietin concentrations after cardiac surgery: Another useful biomarker to be validated

Studies suggest that erythropoietin (EPO) possesses pleiotropic properties [1]. Therefore, we aimed to increase endogenous EPO production in coronary artery bypass graft surgery (CABG) by applying Acute Normovolemic Hemodilution (ANH). However, the hypothesis that ANH would afford cardioprotective effects through increased endogenous EPO, was not confirmed [2]. Subjects in the cardiopulmonary bypass arm were randomized to either a Control (C) or an ANH group. Off pump coronary artery bypass (OPCAB) arm underwent no treatment. After anesthesia induction, in the ANH group blood was withdrawn into a sterile blood bag and replaced by colloids. EPO concentrations were measured before anesthesia, immediately after heparin injection, at the Intensive Care Unit (ICU) arrival and 24 h postoperatively. Table 1 illustrates this evolution. The EPO levels showed a significant increase in the 3 groups at the ICU arrival, but ANH group had significantly higher concentrations compared to the other two arms. At 24 h the values continued to increase. This increase was significant in the C and the OPCAB group, but did not reach a significant difference in the ANH. The latter had already significantly increased its values at the ICU arrival. The short-term outcome of our patients was similar. The question remains if this postoperative EPO might reflect a kind of surrogate marker, which is up-regulated in patients who will develop worsening outcome. Indeed, studies in patients with chronic heart failure have indicated that high endogenous EPO levels may be a predictor of worse long-term outcome [3]. This has also been found in acute coronary syndrome [4]. We do not have any data on the long-term outcome of our patients. Future trials are warranted to evaluate the predictive value of postoperative EPO in cardiac surgery.

References


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Table 1

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Heparin</th>
<th>ICU arrival</th>
<th>24 h Postop</th>
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<tbody>
<tr>
<td>C</td>
<td>7.73(5.77–13.48)</td>
<td>6.71(4.96–11.14)</td>
<td>20.54(11.26–35.12)</td>
<td>55.17(41.01–86.24)</td>
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<tr>
<td>ANH</td>
<td>7.31(4.70–10.82)</td>
<td>6.18(3.37–8.24)</td>
<td>33.74(14.41–60.47)</td>
<td>40.41(22.98–66.12)</td>
</tr>
<tr>
<td>OPCAB</td>
<td>8.68(5.76–11.03)</td>
<td>5.79(4.57–9.67)</td>
<td>9.71(7.08–17.33)</td>
<td>34.84(20.84–59.78)</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th–75th interquartile range).

* Statistically significant difference compared to baseline.

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