The low opioid consumption in Italy depends on late palliative care

In response to disturbing rises in prescription opioid abuse, the Food and Drug Administration has proposed the implementation of aggressive risk evaluation and mitigation strategies. In Europe, the extent of the availability and misuse of prescription opioids were difficult to assess from the data currently available, due in large part to the considerable differences that exist in prescribing patterns and regulations. Indeed, new data released to the public painted a shocking picture of unnecessary pain on a global scale. Governments around the world are leaving hundreds of millions of cancer patients to suffer needlessly because of their failure to ensure adequate access to pain-relieving drugs [1]. However, drug availability is not necessarily a guarantee for an appropriate opioid use. In Italy, for example, legislation changed the prescription modalities and there is now a large availability of opioids, which are free of charge for patients. Unfortunately, the effects of the new law, licensed in 2010, were limited, resembling a previous one. Opioid consumption is still poor, particularly in the Southern Italy, and recognition of pain is suboptimal [2]. The reasons for this predictable failure rely on the low level of knowledge and cultural barriers of health professionals on the use of opioids. But another reason is that consultants of the Minister of Health circumscribed palliative care in the limited range of home care and hospice care, which means in the Italian reality, about 20 days before death [3], assuming that palliative care is equivalent to end-of-life care. This is in contrast to the definition of WHO: ‘Palliative care is … applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications’. Moreover, such experts ignored recent scientific evidence which showed that patients receiving early palliative care had less aggressive care at the end of life and longer survival [4]. Most experts strongly suggest to spread palliative care in other settings, other than traditional home care and hospice, to intercept oncologic patients in their disease trajectory early, for example in high-volume oncologic departments, rather than restricting the action area only in the last weeks of life [5]. Early referral to an interdisciplinary supportive/palliative care team should be recommended. Politicians, commissions and experts should be aware of these scientific indications to plan projects that may have an impact on opioid consumption.

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Embryonic stem cell pathways and chemotherapy response: an unexplored route

Cancer stem cells (CSCs) are a subpopulation of cancer cells with long-lasting tumorigenic potential. CSCs share with embryonic stem cells (ESCs) an unlimited self-renewal potential and a notable phenotypic plasticity which are sustained by common gene expression programs [1]. CSCs have been associated with drug resistance and relapse in most cancer types [1]. Although CSC-specific pathways were shown to mediate chemoresistance in several preclinical studies [2], methodological and conceptual complexity has obstructed the examination of this hypothesis in the clinical setting.

To progress in this aspect, we performed an analysis of clinical and whole genome expression data deposited at Oncomine database [3], looking for correlations between CSC gene expression and patient response to chemotherapy. First, we queried the most established CSC markers: surface molecules CD133 (PROM1) and CD44. We found that high CD44 associates with treatment in breast cancer and acute myeloid leukemia. CD133 has not been mechanistically linked to chemo- and radioresistance, while CD44 might mediate chemo- and radioresistance per se, by regulating reactive oxygen species production [5].

We then asked whether the three main adult stem cell signaling pathways (Wnt, Notch and Hedgehog) are associated with drug response, using pathway-specific gene lists available in Oncomine. We found a positive correlation between Notch and Wnt pathways and a poor response to treatment in breast cancer and acute myeloid leukemia.

references


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Individual genes and gene pathways were selected from Oncomine predefined lists. To find the associations, thresholds were set at a P-value of 0.05 for genes and 0.001 and an odds ratio of 2.0 for pathways. Student’s t-tests were used to analyze differences in gene expression between treatment responders and non-responders in each study.

FOLFIRI, folinic acid, 5-fluorouracil, irinotecan; PCV, procarbazine, lomustine, vincristine; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine.

(Table 1). Conversely, we found an association with good response to induction/consolidation therapy in two independent studies in B-cell acute lymphoblastic leukemia (data not shown), suggesting a distinctive interpretation of the CSC hypothesis for this disease. Finally, the Hedgehog pathway did not yield any association with treatment response. The uneven association between major stem cell pathway did not yield any association with treatment (data not shown), suggesting a distinctive interpretation of gene regulation.

At last, we investigated whether a human ESC gene signature would be a predictor of drug response. We found out that the Oncomine literature defined ESC-specific gene lists are strongly correlated to drug resistance in six studies comprising exclusively colorectal cancer and leukemia (Table 1). On the contrary, the ESC signature associates with drug sensitivity in three breast, two leukemia, one lymphoma and one brain studies (not shown). Therefore, although CSC-like subpopulations have been isolated from most solid tumors and circulating tumor cells, our study suggests that drug resistance may be linked to the CSC phenotype in only a subset of cancers.

ESC pathways have not been investigated as predictive markers of chemotherapy response yet. Our findings suggest that ESC gene expression signatures could hold a higher predictive value for treatment response than stem cell pathways or markers in colorectal cancer and perhaps subtypes of leukemia. Future pharmacogenomic studies should address this issue, identifying the most promising cancer–CSC pathway combinations.

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