Case 2 – Age, behavior and social involvement: barriers to treatment?

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Abstract
Affective disorders can interfere with medical compliance, especially in young cancer patients. We report a case of a difficult young patient with localized Ewing's sarcoma who refused treatment making the prognosis worse.

Key words: affective disorders, compliance, Ewing's sarcoma, young adult patients

Affective disorders are the most common disorders encountered in medical practice [1]. Noncompliance is a complicated phenomenon, and decades of research have attempted to establish associations with variables that can be altered and improved in the course of clinical care. One such variable could be patient depression; affective disorders and personality disorders might be others.

Why do personality disorders worsen noncompliance? It was shown that hope and confidence in treatment are essential contributors to clinical benefit [2]. Personality disorders diminish hope and compliance is almost impossible for a patient who has little confidence in the care provided to him/her.

Moreover, there is a good body of evidence suggesting that family support and social networks are critical to ensure patient adherence to treatment [3]. Personality disorders are often associated with social isolation and exclusion from the patient's psychosocial support networks. Furthermore, these disorders can be associated with cognitive defects that hinder adherence to medical prescriptions (e.g. correct use of take-home therapy, attendance at appointments for the administration of chemotherapy). Randomized trials based on multidimensional models and longitudinal samples are needed to define the role of personality disorders in reducing patient compliance.

The patient, P., was diagnosed with an Askin's tumor at the age of only 19 years. He came alone to his first admission. His father was in jail and his mother had been placed under house arrest; the only caregiver was his 17-year-old girlfriend.

At his first visit, he was told: "Chemotherapy administration requires the placement of a central venous catheter and it is associated with some side effects which we'll now go through". These few simple words were enough for the patient to totally reject treatment. It was impossible for him to accept the meaning of his diagnosis and he was not ready to face the difficulties associated with the prolonged treatment course required for his cancer: chemotherapy was seen as a poison, drug avoidance and contraception were part of his life-style, and sperm banking was unacceptable. He refused placement of a port-a-cath because the scar would have damaged a tattoo he got when his brother died in a car accident. The patient soon became aggressive with the ward staff, refusing admission and leading to a battle that resulted in treatment delay. After several attempts, we managed to persuade P. to start on chemotherapy and tried to make him feel as confortable as possible during his stay in the hospital: only a few doctors were consistently involved in his care, he was allowed a single room, and his girlfriend was always with him, night and day. According to the EURO-E.W.I.N.G 99 study protocol, we managed to administer three cycles of vincrisine, doxorubicine, ifosfamide and etoposide (VIDE); this was well tolerated overall except for grade 1 nausea and asthenia. During his fourth cycle of chemotherapy, because of displacement of his central venous catheter, P. reacted aggressively towards the ward staff again, and despite several attempt to explain to him the importance of chemotherapy in achieving a cure, he rejected any further systemic treatment. Restaging showed a stable disease and P. was referred for surgery in July 2013. The final pathol-

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ogy report showed a poor response to chemotherapy (10% necrosis), positive margins and lymph node involvement. He did not attend any of his follow-up appointments and therefore did not receive any post-operative treatment.

P. came to our attention again in December 2013 because of intense headache. A CT scan showed bilateral pulmonary metastases and a skull bone lesion. It took one month to make P. aware of the seriousness of his clinical condition and to start new treatment. He was managed with different chemotherapy regimens, including gemcitabine and docetaxel, irinotecan and temozolomide, and cyclophosphamide but his disease became rapidly resistant and progressed during treatments. Radiotherapy on the skull helped with pain control. As the disease progressed, P. became more and more anxious and aggressive with doctors, nurses and relatives, forcing us to stop treatment. The palliative care team that took over his care struggled against his poor compliance until the very end. P. died three months after treatment discontinuation.

Before the availability of chemotherapy, the survival rate for patients with Ewing sarcoma was <10%, despite the well-known radiosensitivity of the tumor. With multimodal treatment and new protocols, childhood cancer mortality associated with Ewing sarcoma decreased by more than 50% between 1975 and 2010, and the 5-year survival rate increased from 59% to 78% over the same period for children aged <15 years and from 20% to 60% for adolescents aged 15 to 19 years. Several study protocols of multimodal treatment including chemotherapy, surgery and radiotherapy have shown increased survival in localized disease. One of these is EURO-E.W.I.N.G 99, which showed a significant increase in event- free and overall survival after six cycles of chemotherapy with VIDE followed by local treatment (surgery/radiotherapy) and high-dose chemotherapy [4].

In this case, six cycles of VIDE should have been administered, followed by surgery and chemotherapy along with radiotherapy given the poor prognostic indicators in the pathology report, which would have provided good local control and reduced the risk of recurrence. Unfortunately, both the difficulties associated with giving chemotherapy before planned surgery (only 4 instead of 6 cycles) and the delay in radiotherapy treatment after surgery, because of low patient compliance, resulted in systemic dissemination of the disease.

There is evidence in the literature suggesting that teenagers and young adults (TYA) represent a critical subgroup of patients, who are difficult to engage in treatment and involve in clinical research [5, 6]. Cancer diagnosis in TYA can have a significant impact on neurocognitive and emotional functions and often represents the first lifetime contact with the health system [7]. Therefore, correct management of these patients is crucial, requiring an appropriate setting (both pediatric and adult oncology departments are often inappropriate), support and careful communication.

This case report highlights decreased compliance and may provide new perspectives on approaches that physicians can take to improve doctor-patient relationship and clinical benefit. Assessment of personality and the patient's social network could help to identify at-risk patients who require close monitoring and assistance to achieve adherence to treatment. It would be interesting to investigate the role of early detection of this particular subgroup of patients to see if early treatment of personality disorders could improve the clinical outcome.

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Commentary – The 'lost tribe'

In the most recent years a debate about the specific needs of adolescents and young adults (AYA) with cancer is ongoing in the oncology community. From the oncologist's point of view, the main challenge in facing tumors in this age group comes from the extreme variability of cancer types affecting this population and from the lack of clear evidence coming from the literature data mostly based on studies with strict inclusion criteria if performed in pediatric or adult oncology centers.

The traditional distinction between pediatric or adult chemotherapy treatments sometimes translates in a reduced chance for the young adult of being enrolled in study protocols or to be treated in a less intensive manner when admitted to adult oncology units [1-4].

As the experience of osteosarcoma and Ewing sarcoma clearly show, the histology and not the age should indicate the best treatment. There is a clear evidence that young adults treated according to 'pediatric' protocols have a better chance to survive to their disease [4].

Dealing adolescents with cancer is furthermore burdened by several additional factors that might influence the quality of the care.

Non-adherence to cancer treatment is a common issue with young people, being potentially associated with reduced efficacy, difficulties in toxicities identification and higher risk of recurrence [5-10]. Patients emotional status (i.e. depression), competing obligations and lack of appropriate psychosocial support have been identified as risk factors for non-adherence and should be taken into account in patients' risk assessment. As clearly highlighted in this case report, the diagnostic phase often represents a young person's first contact with healthcare system, and appropriate delivery of information in this context plays a crucial role in establishing an engagement and promote compliance. Selective communication skills are required to work with AYAs: cancer-related details, which are often the focus of communication with adult cancer patients, should be combined with a full range of life-style information, paying attention to age-related issues such as sexuality, alcohol consumption or drug abuse. A further unique challenge is represented by the need of combining the respect of young people's confidentiality while keeping parents adequately informed about their child's treatment and care. Careful communication and management of side effects, availability of a dedicated setting with facilities for AYAs within the hospital can help in promoting adherence.

Recently, a conceptual model to improve participation of AYAs in clinical trials has been proposed, based on the so called 'five As': 'awareness' of teenage and young adult cancers by drug developers, 'available' drugs for study of AYA cancers, application of 'appropriate' age eligibility criteria, 'access' to study in all treatment centres for AYAs and 'acceptable' trial design and research questions to health-care professionals and patients [5]. This model represents an interesting first attempt toward the resolution of a complex but well-recognised issue, with potential influence on AYA patients outcome. Given the rarity of many cancer types affecting AYAs, including bone sarcoma, the involvement of young people in clinical research protocols remains essential and a continuous effort to promote participation to clinical trials should be made [10].

At the same time it is essential to support the young with an adequate psychosocial support and a careful communication, with the view of improving the compliance to the treatment.

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