Paediatric Oncology at the Crossroads: A Call for Change

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Cancer in children is fortunately rare. It was first recognised as a challenge when infectious diseases were increasingly prevented and/or became treatable. The first successes in patient care occurred not with new drugs, but rather with well-known chemotherapeutics from the 1970s onwards [1, 2]. For the treating physicians, the approval status of those drugs was irrelevant. Physicians' focus was successful treatment; these studies were performed in the unique situation that effective drugs already existed. These studies were so successful in adult cancer patients that study participation became standard-of-care in paediatric oncology [3].

In accordance with US Federal law, the Food and Drug Administration (FDA) is not authorized to tell physicians what to prescribe, but it controls the promotional activities of pharmaceutical companies. In 1988, the term “off-label” appeared [4], but the entire discipline of paediatric oncology emerged “off-label” decades before the term “off-label” even existed [5, 6].

There is a fundamental difference between drug approval in general and approval/non-approval in “children” defined as younger than 17/18 years. Approval is based on science and data. But approval/non-approval in “children” is based on a misleading administrative definition [7]. There is no relevant physiological difference between 15- and 16-year-old persons. The physiological difference of 1 year is negligible in adolescents, while the difference of 1 month in babies is not [8].

Chemotherapy exposes the entire body to cell poisons in the hope of killing enough malignant cells so that the body can defeat the remaining cancer cells. Chemotherapeutics are unspecific. This helped when their use in adult cancer patients was transferred to young cancer patients, who have more reserves. Young leukaemia patients survived better than adults [1, 2]. In relation to their bodyweight,

they tolerated higher doses. Then followed the assumption that switching targets would also work with modern anti-cancer drugs. However, modern anticancer drugs are not chemotherapeutics.

Paediatric oncology began in the unique situation that its key drugs existed already and “only” needed to be explored in young patients. In the most frequent childhood malignancy, acute lymphoblastic leukaemia (ALL), about 90% survived in 2000 [6, 9]. Further improvement by fine-tuning chemotherapy became limited.

New drugs were needed [10], but “paediatric” laws have achieved the contrary. First, they triggered FDA-rewarded studies, that were amplified by the European Union (EU) paediatric investigation plans (PIPs) for virtually all new drugs. Now the FDA Reauthorization Act (FDARA) authorises mandatory cancer studies with new anticancer drugs in 0- to 11-year-old patients, copying the EU model back into the USA.

US and EU paediatric laws have divided cancer research in young patients into two streams. One specialises in “paediatric” studies with anticancer compounds that are administratively rewarded or ordered. First FDA-rewarded “paediatric” studies aimed at “paediatric” labels for chemotherapeutics that had been used for decades in combination (“cocktails”), investigating single components of these “cocktails” in administratively defined “children” aged ≤ 21 years. Parents of minors who had relapsed after chemotherapy had been talked into such studies, emphasising that study participation was standard-of-care [3]. Around the year 2000, there was little hope for minors after relapse by use of another round of chemotherapy with just one cytotoxic. The clinical studies performed earlier by paediatric oncologists were reasonable with therapeutic intentions [1, 11]. The FDA-rewarded “paediatric” studies lacked clinical intentions. They aimed at “paediatric” labels.

Another FDA-rewarded randomised “paediatric” study investigated nasopharyngeal carcinoma (NPC) in patients aged ≤ 21 years, comparing chemotherapy with chemotherapy plus docetaxel. The publication describes NPC as a paediatric disease [12], which is untrue [13, 14]. This study

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aimed at a 6-month patent extension (“paediatric exclusivity”) [15]. Its winners were the sponsoring company, the researchers, and the FDA. Its losers were the patients and their parents.

PIP-triggered studies include “paediatric” studies with ribociclib in patients aged ≤ 21 years with various cancer types [16]; two “paediatric” melanoma studies that were terminated because recruitment waned as the PIP-demanded monotherapy was below standard-of-care [17, 18]; a “paediatric” temsirolimus study in patients aged ≤ 21 years with various cancer types [19], two “paediatric” sonidegib studies in patients aged ≤ 18 years with various cancer types [20], and a “paediatric” study adding bevacizumab to chemotherapy in patients aged 6 months to < 18 years [21]. Why should cancer types that occur before and after the 18th or 21st birthday react differently to the same compound before and after the 18th/21st birthday? These studies had no positive outcome. Their entire rationale was flawed. They did not help. The melanoma studies even caused harm with treatment below standard-of-care [17, 18]. Nobody has apologised [18].

PIP-triggered studies are financed by pharmaceutical companies as an “entrance fee” into the EU market. A coalition of FDA/EMA, clinical researchers, pharmaceutical companies and commercial clinical research has been formed, allowing and justifying “paediatric” careers in these institutions.

Many cancer types frequently found in adults can occasionally affect patients before their 18th birthday. Conventional melanoma in a 15-year-old patient is not “paediatric” because s/he is legally still a child [18, 22]. Thirteen EU PIPs demand “paediatric” studies in various cancer types including melanoma [18]. PIP-triggered studies recruit worldwide. Leukaemia in a 25-year-old is fundamentally not different from leukaemia in a 15-year-old. Also PIP-demanded “paediatric” leukaemia studies are questionable [6, 7, 18].

Before FDARA, the FDA could not mandate studies in rare diseases. All paediatric cancers are rare [1]. FDA/EMA-triggered “paediatric” cancer studies are based on a flawed rationale, making empty promises towards patients, parents, and politicians. This is covered by the law. It is an extraordinary and historically unique situation that the law justifies studies that range between useless, exaggerated, and harmful. All these studies recruit worldwide [23–25].

US FDARA translates the fear and despair of parents and the hidden conflicts of today’s main players of “paediatric” oncology into a system of empty promises. “Something” is done, but it is useless. This waste of funds and energy jeopardises public trust in science, research, education and authorities.

Cancer treatment changed with targeted therapies: since imatinib, chronic myelogenous leukaemia is no longer

lethal. CAR-T cell therapy against relapsed/refractory ALL can help the 10% who until recently were doomed.

Emily Whitehead contracted ALL when she was aged 5 years. She went through routine chemotherapy and relapsed. Her parents enrolled her in a reasonable study, blood was taken, her T-cells were re-programmed to attack ALL cells, and were re-infused. A cytokine storm with high fever was successfully treated with tocilizumab. Emily recovered. Today, she is healthy and cancer free [26–28]. She was lucky, being referred to a reasonable study. Had she entered one of the many PIP-demanded studies, she would likely be dead. Reasonable studies that are based on a truly scientific rationale and test advanced treatment compete for patients with EMA/FDA-triggered questionable studies [6, 7, 18, 23–25].

The term “paediatric” oncology is not based on science. It is administrative. When a 15-year-old with conventional melanoma is admitted to a hospital, administrative rules decide into which ward s/he will be placed. But his/her cancer is neither “paediatric” in a paediatric ward nor adult in an adult ward [18, 22]. Treatment should be the same.

Paediatric legislation has changed the position of paediatric oncology from a niche towards a voice to be heard. This was a political transformation. This was perceived as a step forward, but became an obstacle against further progress.

The FDA has partially stepped back from “paediatric” cancer studies. It now recommends that adolescents be included in adult cancer studies [29], thus admitting that all “paediatric” cancer studies in 12- to 21-year-old patients since 1997 were useless and worse. The FDA has shown some flexibility without abandoning the concept of children as “therapeutic orphans” and “paediatric drug development” [30]. The EMA has progressed further into regulatory dogmatism, now considering liver and intrahepatic bile duct carcinoma, and kidney and renal pelvis carcinoma as “paediatric” diseases and demanding PIPs for these malignancies that occasionally occur in patients before their 18th birthday [31].

“Paediatric” cancer is not defined by transparent scientific terms, but as what is seen by paediatric oncologists, which is circular. Leading journals report on “paediatric” cancer; the examined tissue is from patients ≤ 25 years of age [32]; 98.5% of tissue from patients ≤ 20 years of age (no upper age limit for the rest) [33]; “paediatric” cancer defined as in patients ≤ 14 years of age [34]. The genomic alterations described in these papers would not justify business investments, but they are used to justify FDA/EMA-mandated studies [32–35].

Clinical oncology, regulatory authorities, and industry have so far not addressed the difference between legal and administrative classification of young persons as “children”. Malignant cells are malignant. Period. Types of malignancy

differ across age groups. Their clinical course differs in different ages, but they are not entirely different diseases.

It is likely that the FDA/EMA-triggered “paediatric” studies in cancer and other diseases are the largest patient abuse in medical research history [9]. Clinical studies with therapeutic intentions compete for patients with questionable studies. Science and medicine must tackle this challenge, or public trust will be jeopardised.

Declarations

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