

RETINOBLASTOMA: AN EXEMPLARY TUMOUR IN YOUNG CHILDREN THAT CAN BE CURED IN LOW-INCOME COUNTRIES

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Cancer will be one of the major health challenges worldwide in the next few decades. Among all the different types of this ubiquitous disease, cancer in children must be among the priorities in action plans to combat cancer in low- and middle-income countries. Among childhood tumours, retinoblastoma appears to be a good example as it is now curable in over 95% of cases in high-income countries due to early diagnosis and quick access to a competent multidisciplinary team. Relying on the experience of Institut Curie in Paris (the reference centre for all retinoblastoma cases in France), we have developed a programme to help local teams in some sub-Saharan French speaking countries (these currently include Mali, Democratic Republic of Congo, Senegal and the Ivory Coast, and soon in Madagascar) to become national or regional reference centres promoting early diagnosis campaigns, offering all treatment facilities including conservative treatments and rehabilitation after enucleation.

Low-income countries, particularly French-speaking sub-Saharan African countries, still have a very young population with at least 40% aged less than 15 years old with a low life expectancy, around 50, and a fertility index still high around 5. So cancer in children younger than 15, even if the incidence rate is nearly the same, represent a higher proportion of the population in these countries (about 5% of all cancers) than in high-income countries (now less than 0.5% in France). We know that the number of cancers in adults will rapidly increase in the future¹ due to ageing of the population and changes in lifestyle. Many countries are not prepared in any way to face this new challenge: the complexity of caring for a growing number of patients with cancers which require so many different skills from so many different actors working closely together.

The situation will be complicated in low-income countries by the fact that at the same time, other health problems such as maternal and neonatal mortality, malnutrition and

infectious diseases will not be totally under control and that other non-communicable diseases like diabetes and cardiovascular diseases will also take more and more room increasing difficulties to find funding.²

Therefore, as everything cannot be achieved at the same time, more than ever, each country has to define its health priorities in oncology according to:

- ▶ Where it is regarding oncology indicators (incidence, mortality, types of tumours observed, existing infrastructure, number of oncology specialists for treatment and diagnosis, number of trained people providing supportive care of cancer patients, etc).
- ▶ What are the best cost-benefit ratios in terms of a reduction in mortality and morbidity for different interventions (prevention, early diagnosis, pathology, diagnostic imaging, surgery, radiation therapy, medical treatments, supportive care) to fight the different types of cancer.

It is essential that all these priorities are broken down into a multi-annual action plan. Many cancers in children are good candidates to be prioritized in all developing countries³, as the cure rate is now over 80% in high-income countries with costs of care often much less than for most of cancers in adults.

We have chosen to define and implement a programme called: "Supporting early diagnosis, treatments and the rehabilitation of children with retinoblastoma in sub-Saharan African countries" based on the following assumption shared by different authors⁴: "with early diagnosis, rapid care by a specialized team, treatment is simpler, less expensive, with higher cure rates and with less after effects".

There are different reasons for this choice:

- ▶ Retinoblastoma is now the most easily curable tumour as the 10-year cure rate is more than 95% of cases in high-income countries.⁵ This is obtained with a relatively low cost resources but thanks to early diagnosis and easy access to specialized teams. But, the cure rate is still low (between 20% to 60%) in low-income countries.⁶ So retinoblastoma seems to be a good candidate to demonstrate that coordinated action is able to quickly change the situation in low-income countries.
- ▶ In 2010, we had discussions with the French-African paediatric oncology group (GFAOP). This organization set up by Professor Jean Lemerle 10 years ago, has supported the establishment and the operation of 13 pilot paediatric oncology units in 10 French-speaking sub-Saharan African countries (www.gfaop.org). Through GFAOP, common protocols were developed by "committees". Retinoblastoma was discussed by the "retinoblastoma committee" led by the Bamako team from Mali (F Traoré and F Sylla). We had meetings in France and in Bamako in 2010 and 2011.
- ▶ The Institut Curie is the reference centre in France for retinoblastoma care and research with a specialized multidisciplinary team (ophthalmologists, paediatric oncologists, radiation oncologists, pathologists, imaging specialists, geneticists, biologists, supportive care specialists and researchers). Almost all the French retinoblastoma cases (50 new cases per year) are managed by Curie Hospital. Many research projects are conducted through the Curie research centre.
- ▶ The Alliance Mondiale Contre le Cancer (AMCC), French branch of the International Network for Cancer Treatment and Research (INCTR), is a small NGO directed by Pierre Bey, who was a former director of the Institut Curie Hospital, and decided in 2010 to make this "retinoblastoma programme" one of its flagship projects.
- ▶ We also had the advantage through INCTR of benefitting from the experience of Sidnei Epelman⁷ who developed a successful retinoblastoma early detection campaign in Brazil.
- ▶ Financial support for this programme came from the Sanofi Espoir Foundation (www.fondation-sanofi-espoir.com) through the "My Child Matters" programme, from Retinostop (a French NGO created by parents of children with retinoblastoma, www.retinostop.org), from the French Ministry of Health, from GFAOP and Lalla Salma Foundation (for chemotherapy), from INCTR and from the Institut Curie.

The existing situation of retinoblastoma in Mali was known:^{8,9}

- ▶ 55 cases were reported between 2005 and 2007 which represented 33% of the 166 solid tumours seen during this period (while retinoblastoma represented only 4.2% of solid tumours in children in France).
- ▶ The median age at diagnosis was 4.2 years (versus 2 years in France).
- ▶ 60% of cases with extra-ocular extension at diagnosis (0% in France in the last five years).
- ▶ 30% of patients who did not receive the entire prescribed treatment (versus 0% in France).

We observed many reasons for this situation that were very close to the description given by T Eden¹⁰ of the main obstacles to be overcome to improve care of children with cancer in the developing world: poverty, other societal priorities, lack of registration (retinoblastoma is probably over-represented in Africa due to the under-estimation of many other deep seated tumours), lack of awareness, lack of access to diagnosis and treatment facilities, lack of trained staff and infrastructure problems. For retinoblastoma in Mali, we can also add cultural factors and the absence of access to ocular prosthesis and to effective conservative treatments¹¹ which are important reasons for parents to refuse enucleation of the affected eye, particularly if the diagnosis is made early.

We decided to develop the programme in Bamako because some of the prerequisites were fulfilled:

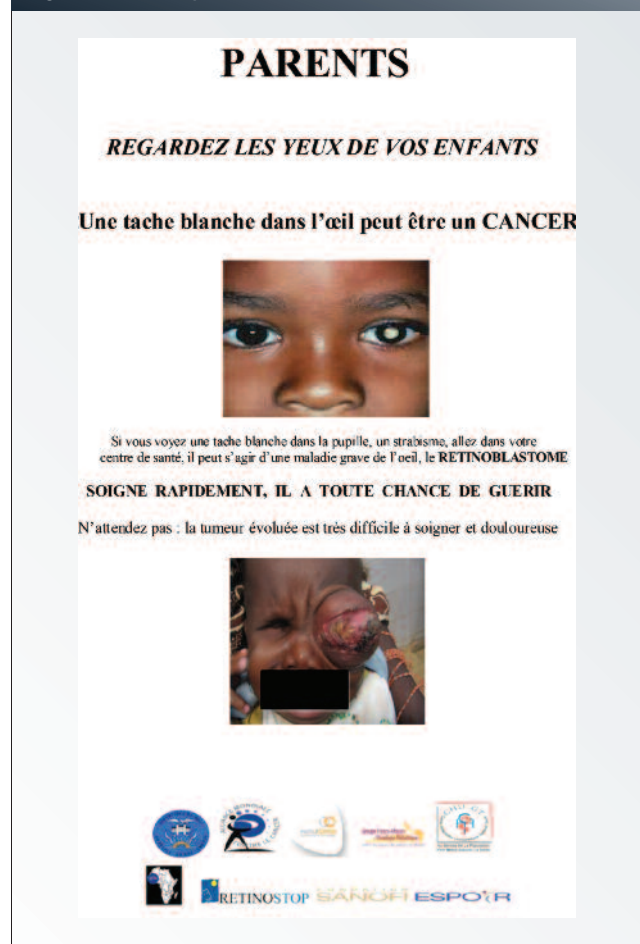
- ▶ There were core skills available with a paediatric oncology unit (in the paediatric department of Gabriel Toure University Hospital, headed by Professor Boubacar Togo) supported by GFAOP and an ophthalmologic institute (IOTA, Institute of Tropical Ophthalmology for Africa) close by.
- ▶ The doctors caring for children with retinoblastoma (paediatric oncologist Dr Fousseyni Traore and

ophthalmologist Dr Fatoumata Sylla) had the determination to change the situation with the support of their department heads.

The programme included:

- ▶ Approval by the authorities, particularly by the ministry of health and by the directors of the hospitals (for Bamako, the University Hospital Gabriel Touré and IOTA).
- ▶ Improvements in early diagnosis with:
 - Information in health centres for doctors (general practitioners and paediatricians) and other health personnel (nurses, midwives, technicians) on the symptoms of retinoblastoma (leukocoria and strabism), training for ophthalmologists (36 in Mali with two-thirds of them in Bamako) and for ophthalmology technicians (113 in Mali in regional hospitals and some health centres) in the identification of suspected cases for referral to IOTA.
 - Information for all parents using posters (Figure 1) designed from existing models in France and Brazil and also through national campaigns to fight blindness on radio and TV in French and in the Bambara language.
 - An effective response at different stages of care in developing the capacity to take rapid and effective action. This means ensuring:
 - access to a specialized ophthalmologic consultation at IOTA for children with suspected retinoblastoma with the possibility of retina examination (ocular fundus) in less than one week;
 - access to ocular ultrasound and CT-scanning and NMR imaging (when possible in Bamako);
 - the possibility of surgery (enucleation) at the early stage in less than a week;
 - systematic ocular prosthetic rehabilitation (training of a person on site and at the Prothelem company in Paris);
 - consolidation of pathology (training of a pathologist for paediatric oncology pathology in Paris with the help of GFAOP);
 - when necessary, access to chemotherapy (through GFAOP by providing the necessary cancer drugs) and to radiotherapy (when available in Bamako);
 - the establishment and development of conservative treatments for bilateral cases (training of an ophthalmologist in Institut Curie, Paris, for thermo-chemotherapy techniques, and the acquisition of necessary materials such as a laser) with the possibility of follow-up under general anesthesia for ocular fundus.

Figure 1: Poster for parents



- ▶ Financial support for the poorest families (to limit treatment interruptions).
- ▶ Facilitating research activities around retinoblastoma (beginning with epidemiological studies on the true incidence of retinoblastoma and on the identification of specific risk factors) through the network of reference centres established in sub-Saharan French-speaking countries treating nearly 200 new cases per year by the end of the programme.
- ▶ Systematic registration of all cases of retinoblastoma from a common chart between paediatric oncologists and ophthalmologists with regular evaluations according to previously defined indicators (this was embodied in inter-institutional agreements supported by the French Ministry of Health).

The programme was officially launched in Bamako on 5 November 2011, during a visit from professionals including an ophthalmologist, a radiation oncologist, a paediatric oncologist and an ocular prosthetist. Over three days, the programme was finalized: there were discussions with the authorities, a course on retinoblastoma and a formal meeting

Figure 2: The first ocular prosthesis being performed in Bamako, Mali



attended by the press. During this visit, after two days of training, the first ocular prosthesis was carried out at IOTA (Figure 1).

From October 2011 to October 2013, 68 new cases of retinoblastoma in children were diagnosed and treated (despite a war in the north of the country) by the Bamako multidisciplinary team (15% came from neighbouring countries). It is too early to have a clear assessment of the evolution of the stages at diagnosis with time, but only 40% had advanced disease at presentation (versus 60% in the historical series 2005–2007). Of the 30 intraocular unilateral cases, 85% are now in complete remission. All enucleated children in this new series received an ocular prosthesis. Conservative treatment for bilateral cases will be available in early 2014.

It was decided to extend the programme in other countries and Lubumbashi in the Democratic Republic of Congo was chosen on the same criteria:

- ▶ The availability of core skills through a paediatric oncology unit supported by GFAOP, located in the

University Clinics of Lubumbashi, close to the ophthalmology department.

- ▶ That the doctors engaged in the care of retinoblastoma (paediatric oncologist Dr R Lukamba, ophthalmologist Professor G Chenge and pathologist Professor J Ilunga), had the support of the authorities of the hospital, the university and the province of Katanga.

The programme was officially launched on 5 December 2012, with a conference in the faculty of medicine at Lubumbashi with an audience of 250 people. This took place during a visit like the first one in Bamako. The training of an ophthalmologist and of a technician for ocular prosthesis was undertaken in Paris early in 2013.

For these two centres, regular follow-ups were organized by conference call.

The programme continues to expand and visits, on the same basis, were conducted in October 2013 in Dakar (Senegal) and in Abidjan (Ivory Coast). Next year, we plan to implement a programme in Madagascar and probably later in one or two other countries.

So, finally, we plan to cover about 200 new cases of retinoblastoma each year (out of at least 2,000 appearing each year in the whole of Africa) and hope to reduce the mortality which was about 70% to less than 30% and to reduce blindness and other after-effects.

This may seem like a drop in the ocean, but we think that retinoblastoma, even if it is not a health priority according to its scarcity, is a special tumour, the only one curable in almost 100% of cases, whereas in the absence of treatment death occurs after a spectacular and painful evolution. We are convinced that the success of such a programme will go far beyond this single tumour and will benefit the entire fight against childhood cancer. ●

References

¹ Bey P. Le cancer en Afrique. *Bull Cancer* 2013; 100 : 112-3

² Magrath I, Bey P, Shad A, Sutcliffe S. Cancer funding in developing countries: the next health care crisis? *Lancet* 2010; 376: 1827

³ Magrath I, Stellarova-Foucher E, Epelman S, Ribeiro R, Harif M, Li CK, Kebudi R, Macfarlane SD, Howard S. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol* 2013; 14:e104-16

⁴ Rodriguez-Galindo C, Wilson MW, Chantada G et al. Retinoblastoma : one world, one vision. *Pediatrics* 2008; 122: e763-70

⁵ Aerts I, Sastre-Garau X, Savignoni A, Lumbroso-Le Rouic L, Thebaud-Leculée E, Frappaz D, Coze C, Thomas C, Gauthier-Villars M, Lévy-Gabriel C, Brisse HJ, Desjardins L and Doz F. Results of a prospective study on the postoperative treatment of unilateral retinoblastoma after primary enucleation. *J Clin Oncol* 2013; 31: 1458-63

⁶ Chantada GL, Qaddoumi I, Canturk S, Khetani V, Zhigui Ma, Kimani K, Yenid B, Sultan I, Sitorus RS, Tacyildiz N and Abramson DH. Strategies to Manage Retinoblastoma in Developing Countries. *Pediatr. Blood Cancer* 2011; 56: 341-8

⁷ Epelman S. Preserving vision in retinoblastoma through early detection and intervention. *Curr Oncol Rep* 2012;14: 213-9

⁸ Boubacar T, Fatou S, Fousseyni T, et al. A 30 month prospective study on the treatment of retinoblastoma in the Gabriel Toure Teaching Hospital, Bamako, Mali. *Brit J Ophthalmol* 2010; 94: 467-9

⁹ Traoré F, Togo B, Sylla F, Cheick TB, Diakité AA, Dicko-Traoré F, Sylla M, Sidibé T, Doz F, Harif M, Bey P, Desjardins L. Le rétinoblastome: état des lieux au Mali et programme d'aide au diagnostic précoce, aux traitements et à la réhabilitation. *Bull Cancer* 2013; 100 : 161-5

¹⁰ Eden T. Curing paediatric cancer in the developing world. *Cancer Control, Global Health Dynamics* 2013; pp 104-7

¹¹ Lumbroso-Le Rouic L, Aerts I, Levy-Gabriel C, Dendale R, Sastre X, Esteve M, Asselain B, Bours D, Doz F, Desjardins L. Conservative treatments of intraocular retinoblastoma. *Ophthalmology* 2008; 115: 1405-10