Second malignant neoplasms after AML in Great Britain 1970-2000

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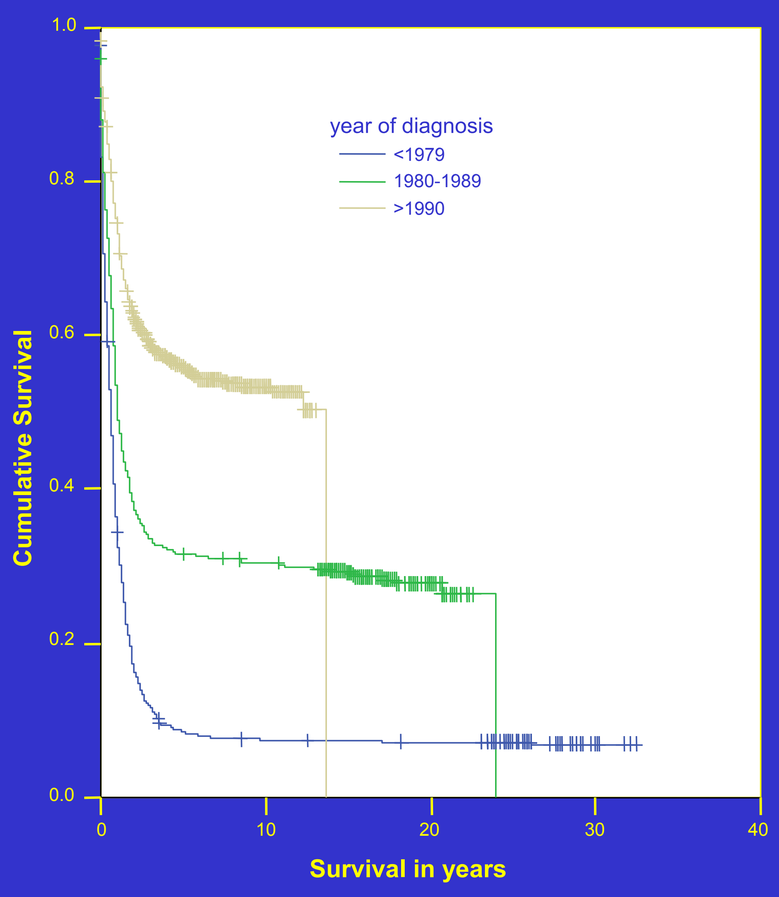
Introduction

The advent of intensive therapy for childhood acute myeloid leukaemia (AML) has improved survival for these children to 50% or more in recent studies(1-3), see figure for UK survival. There are now increasing numbers of long term survivors of this treatment and it is important to quantify the risk of late effects. In the UK the majority of children with AML have been treated on one of the national AML trials (3) which have consisted of intravenous anthracycline-based chemotherapy and a short course of intrathecal therapy for central nervous system prophylaxis, with allogeneic stem cell transplant if a donor is available. Very few articles have focussed on the occurrence of second malignancies after childhood AML. Leung et al(4) reported a cumulative incidence of 1.34% (+/- 0.6%) at 15 years with a standardised incidence ratio (SIR) of 10.6(95% CI 3.3-22.3)based on 5 cases treated between 1970 and 1996, Neglia (5) reported an SIR of 7.9(3.6-15.0) based on 9 cases treated from 1970-1986. In a NOPHO report (6)of long term results of childhood AML treatment since 1984 there was no mention of second malignant neoplasms. We undertook the current study to estimate the risk for children treated for childhood AML in the UK.

Survival of children diagnosed with AML in UK



Methods

The population-based National Registry of Childhood Tumours was searched for subsequent malignant neoplasms (SMN) among cases of AML diagnosed from 1970-2000. Pathology reports were sought from treating hospitals to confirm diagnosis of SMN. Cases were excluded if the diagnosis of the second tumour was within a year of AML diagnosis. A standardised incidence ratio was calculated using population expected numbers of tumours for children of the same age*, and cumulative incidence was calculated using Kaplan-Meier survival methods. Follow up was to the end of 2002.

*The number and type of tumours were compared with the background rate of these tumours in the population of England -"expected rates" which were obtained from the Office of National Statistics (ONS) covering the years 1971-2002 and classified into the same categories as the observed cases.

Case	Treatment	Age at AML diagnosis (yr)	Second Tumour	Period since AML (years)	Outcome
1	Chemotherapy plus stem cell transplant with total body irradiation (tbi)	11	occipital dural sarcoma	3.5	Third tumour breast cancer 16 years from AML. Died 20 yr from AML
2		13	cholangiocarcinoma	18.2	Died 19 yr from AML
3		14	papillary carcinoma thyroid	19.0	Alive 24 yr from AML
4		9	papillary carcinoma thyroid	13.7	Alive 21 yr from AML
6		6	round cell sarcoma pelvis	7.3	Died 7.4 yr from AML
7		9	papillary carcinoma thyroid	7.8	Alive 16 yr from AML
8		10	osteosarcoma thoracic spine	8.9	Died12 yr from AML
5	Chemotherapy alone	3	Ewing's sarcoma tibia	5.0	Died 15 yr from AML having had a soft tissue Ewing's sarcoma in other leg 6 years after 1st
9		1	parotid mucoepidermoid carcinoma	10.0	Alive 15 yr from AML
10		4	alveolar rhabdomyosarcoma of perineum	2.5	Died 4 yrs from AML

Results

There were 2396 cases of AML diagnosed among children aged under 15 years between 1970 and 2000 contributing 8499 person years of follow up. Two cases were excluded because the diagnosis of the second tumour was so close to that of the first (one case of neuroblastoma found at post mortem examination and the second was a case of brain stem PNET 3 months from AML diagnosis). Another was excluded because the original diagnosis of AML was changed to acute lymphoblastic leukaemia(adenocarcinoma of small bowel 16 years from first cancer)

Ten survivors developed SMN. Two from the period 1970-1979, four each from the periods 1980-1989 and 1990-1999. The SIR for all SMN combined was 6.0 (95%CI 2.9-11.0). The cumulative incidence of a second malignancy was 3.7% by 20 years. The most frequently observed second tumour was papillary thyroid carcinoma and the 3 individuals with these tumours had all received stem cell transplant (SCT) with total body irradiation. In all cases the stem cell transplant was carried out within a year of the AML diagnosis and in all but one by 6 months. The three cases who developed a second malignancy without having received SCT were the youngest and all less than 5 years of age at diagnosis.

Discussion

Although a wealth of knowledge is accumulating about the risk of second malignant neoplasms among survivors of childhood cancer generally very few papers give specific risks for childhood AML survivors. The reason for this is that until recently the percentage of survivors has been small.

Many papers have reported an increase in SMN after SCT with cumulative incidence of 11% (2.3-19.8) (7) with young age and tbi being particular risks factors. A high incidence of thyroid malignancy is a recurrent theme (8;9) also brain or CNS tumours(10). Papers tend to refer to radiation therapy as being the key risk factor for many of tumours, however our case of mucoepidermoid carcinoma of the salivary gland occurring after chemotherapy is not alone - this has also been described by Leung and Whatley (11). This study confirms that survivors of childhood AML are not at a particularly great risk from second malignancy - Jenkinson (12) gives an SIR of 6.2 among 16,541 3 year survivors of childhood cancer treated in Britain up to the end of 1987.

Conclusion

Continued follow up of children treated for AML is required for many reasons, particularly the possibility of cardiotoxicity. It is reassuring to know that the risk for second malignant neoplasm seems small, but particular attention should be given to those treated at a young age or receiving SCT.

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