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Early secondary leukaemia following chemotherapy for advanced small-cell carcinoma lung

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ABSTRACT

Secondary leukaemia is an uncommon and serious complication of chemotherapy for various malignancies. The most common offending drugs are alkylating agents and topoisomerase II inhibitors. Two to twelve percent of patients (pts.)who receive etoposide based chemotherapy develops secondary acute myeloid leukaemia (AML). AML following etoposide based treatments most likely occur within 3 years after treatments, and the mean latency period from drug administration to the onset of secondary leukaemia is about 2 years. Here we presenting an interesting case report of a 65 years old male diagnosed as small cell lung cancer (SCLC), treated outside with etoposide based combination chemotherapy developed early secondary leukaemia within 15 months of iniation of treatment.

INTRODUCTION

SCLC accounts for approximately 15% of all bronchogenic carcinomas. At the time of diagnosis, approximately 30% of pts. have tumours confined to the hemi-thorax of origin, the mediastinum, or the supraclavicular lymph nodes. These pts. are designated as having limited-stage disease (LD). [1] Pts with tumours that have spread beyond the supraclavicular areas are said to have extensive-stage disease (ED). SCLC is more responsive to chemotherapy and radiation therapy; however, a cure is difficult to achieve because of greater propensity to widely dissemination.The chemotherapy regime for pts. with ED-SCLC is commonly given as two-drug combination of platinum and etoposide. [2] Common side effects of etoposide are hair loss, vomiting, nausea, diarrhea, loss of appetite infection, anemia, bruising, bleeding, and rarely may cause oto-toxicity, nephrotoxicity and dreadful secondary leukemia. Here we are presenting a case report of a pt of ED-SCLC who had already received a total cumulative dose of etoposide 2400 mg/m^2 and carboplatin 3600 mg/m^2 during a period of 15 months outside and was referred to us for maintenance chemotherapy. On blood evaluation prior to maintenance chemotherapy, pt's had leucocytosis and differential leukocyte count (DLC) revealed atypical cells. Bone marrow examination was done and was suggestive of AML.

CASE REPORT

A 65 years old diabetic and hypertensive male presented with complaints of cough and breathlessness since 15 days in May 2013. CECT thorax, dated 21st May, 2013 reveals interstitial lung disease with right (Rt) sided pleural effusion (PE) and nodular thickened enhanced parietal pleura. Computerised Tomography (CT) guided fine needle aspiration cytology (FNAC) from pleural nodule was suggestive of (s/o) poorly differentiated malignancy. On Immuno histo chemistry (IHC) the tumor cell express CD56, CK (granular positivity), and CK7 (focal weakly positive). On Positron Emission Tomography (PET)-CT dated May 29, 2013 reveal metabolically active Rt. lung lesion with pleural and lymph node involvement. Pt was diagnosed as case of extensive Rt SCLC and was planned for 6 cycle chemotherapy, with etoposide and carboplatin, repeated 3 weekly followed by prophylactic cranial irradiation (PCI). Post 3 cycles of chemotherapy repeat PET-CT in August, 2013 s/o partial response to treatment and metabolically active residual disease. Then he continued 3 more cycle of chemotherapy completed in September, 2013 followed by PCI with 24 Gy in 12 fractions from October 12, 2013 to November 4, 2013. On PET-CT dated December, 2013 s/o stable disease after which he was kept on follow up.

On follow up, 6 month post treatment PET-CT was done in June, 2014 which was s/o progressive disease with hypermetabolic hyperdense lesion in left temporal lobe brain. Bone marrow aspiration cytology (BMAC) reveals infiltration by metastatic cells. In view of progressive disease and poor performance score pt was started on weekly etoposide 100mg/m^2 and carboplatin 150 mg/m^2 on day1, day8 and day15 repeated 3

weekly for 3 cycle. He completed 2 cycles on July 8, 2014 and referred to us for third cycle of planned chemotherapy. On routine blood investigations dated August, 2014, pt had severe anaemia (Hb-6gm %), thrombocytopenia (platelet count-10,000/µl)and leucocytosis (total leukocyte count-27,000). Blood smear showed presence of atypical cells which was further evaluated by bone marrow examination. BMAC dated august 2nd, 2014 revealed hypercellularity with marked suppression of normal haematopoiesis and extensive infiltration by blasts (51%). Myeloid series show preponderance of blasts 2.5 times larger than small lymphocytes with granular cytoplasm showing Auer rods suggestive of AML. An opinion from medical oncologist was taken and possibility of drug induced leukaemia was made. Further evaluation couldn't be performed because of poor general condition of pt and despite of all supportive treatment he succumbed to death within a week.

DISCUSSION

Drugs that induce secondary leukaemia comprise alkylating agents, topoisomerase II inhibitors, and anthracycline agents. Etoposide is a DNA topoisomerase II inhibitor widely used for the treatment of many types of cancers. [3,4]. However, etoposide has been associated with an increased risk of secondary leukaemia. Ratain et al. in 1987 first propounded the relationship between etoposide and secondary leukaemia when it was used for advanced non-SCLC [5]. Subsequently, several investigators reported secondary leukaemia, particularly acute AML, when etoposide was used to treat lung cancer, non-Hodgkin lymphoma, neuroblastoma, acute lymphoid leukaemia (ALL), wilms tumor, rhabdomyosarcoma and germ cell tumour (testicular tumour)[6-7] Generally the leukaemia following etoposide-treatments are likely to occur within 3 years after treatments, and the mean latency period from drug administration to the onset of secondary leukaemia is about 2 years. Between 2 and 12% of pts that receive etoposide develop secondary AML. The prognosis of alkylating-agent-induced secondary leukaemia appears to be worse than that for spontaneously occurring leukaemia and the prognosis of etoposide-related secondary leukaemia is extremely poor.The risk of secondary AML appears to be dependent on both treatment schedule and dose. The 4- to 5-year cumulative risk of the complication has ranged from 0% to 18.4% in pts treated with cumulative dose ranging from 5,200 mg/m2 to 19,200 mg/m2 [8]. Currently, low-dose, chronically administered regimens are more commonly given to pts with refractory or relapsed cancers; however, it is difficult to assess the risk of drug-induced AML associated with this regimen due to the short survival period.Furthermore, additional factors influence the risk of etoposide-related secondary leukaemia, like concomitant radiotherapy or combination of high-dose platinum agents, like cisplatin or carboplatin. [9]

Currently, intense strategies are being developed, including stem-cell transplantation, to treat MLL-rearranged acute leukaemia, but the outcome has remained poor. More recently, the National Cancer Institute/National Institute of Health Developmental Therapeutics Program (NCI/NIH) proposed testing an approved set of drugs designed to combat MLL-rearranged paediatric leukaemia cell lines [10].

CONCLUSION

Etoposide is an efficient anticancer agent,however due to increase survival and overall cure rate of cancer pts, interest has arisen on the potential risk for therapy induced secondary leukaemia. It is necessary to follow up all the pts receiving long duration of chemotherapy for early diagnosis of secondary leukaemia.It's time to think of a better option for treating primary malignancy with regards to schedule and dosing of chemotherapy to avoid development of secondary malignancy and improve survival of pts.

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